U.S. PUBLIC HEALTH PREPAREDNESS FOR SEASONAL INFLUENZA: HAS THE RESPONSE IMPROVED?

HEARING

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

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C O N T E N T S

WITNESSES

SUBMITTED MATERIAL

U.S. PUBLIC HEALTH PREPAREDNESS FOR SEASONAL INFLUENZA: HAS THE RESPONSE IMPROVED?

THURSDAY, NOVEMBER 19, 2015

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 9:59 a.m., in room 2322 Rayburn House Office Building, Hon. Tim Murphy (chairman of the subcommittee) presiding.

Members present: Representatives Murphy, Griffith, Bucshon, Flores, Brooks, Mullin, Hudson, Collins, Cramer, DeGette, Castor, Kennedy, Green, and Pallone (ex officio).

Staff present: Rebecca Card, Assistant Press Secretary; Brittany Havens, Legislative Associate, Oversight; Charles Ingebretson, Chief Counsel, Oversight and Investigations; Graham Pittman, Legislative Clerk; Chris Santini, Policy Coordinator, Oversight and Investigations; Alan Slobodin, Deputy Chief Counsel, Oversight and Investigations; Waverly Gordon, Democratic Professional Staff Member; Tiffany Guarascio, Democratic Deputy Staff Director and Chief Health Advisor; Christopher Knauer, Democratic Oversight Staff Director; Una Lee, Democratic Chief Oversight Counsel; and Elizabeth Letter, Democratic Professional Staff Member.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY. Good morning. We have the subcommittee hearing from Oversight and Investigations. Earlier this year, in February, this subcommittee held a hearing on last year's flu vaccine mismatch. This mismatch to the predominant flu virus resulted in more deaths and hospitalizations because of the vaccine's lower than usual effectiveness.

Today, we are returning to that issue to discuss what our public health agencies have learned in the intervening months. I want to thank my friend, the Ranking Member Diana DeGette of Colorado, for her assistance and continued passion on this important topic. We work closely on this issue sending bipartisan letters and receiving briefings, not only on this year's flu vaccine, but also on our broader response to seasonal and pandemic flues.

Influenza is a leading cause of death in the United States, especially in a severe flu season. Each year, millions of Americans re-

ceive flu shots to help protect against the illness. Getting a flu shot is important. Even in a bad flu season, the vaccine can reduce the symptoms and duration of the flu, and I encourage everyone who has not already received a flu shot this season to get one, even if the vaccine is not perfect.

Last year, the United States experienced a severe flu vaccine mismatch and public health officials designed the vaccine based on information available in February. But the virus mutated before the flu season began resulting in an effectiveness rate of only 19 percent of the vaccine and even lower for senior citizens.

We have learned, however, that even in a good year, the effectiveness of the vaccine is lower than it should be. In 4 of the last 10 years, the flu vaccine effectiveness rate fell below 40 percent and it is clear that the seasonal flu can cause severe public health impacts on the same scale as a pandemic flu.

The time for an updated approach to dealing with the flu has long passed. The committee's oversight work has made a difference. The Department is now treating the seasonal flu as a high priority. Tools and plans typically reserved for pandemic flu situations are being considered in the fight against the seasonal flu.

An HHS Influenza Working Group has compiled 13 issues and recommendations to improve the influenza vaccine development and manufacturing process. They are working to improve surveillance, utilize technology to speed vaccine production, and make more effective vaccines. But there is still much work to be done.

The issues surrounding the flu vaccine are not new. We are still largely manufacturing flu vaccines and detecting flu virus changes with technology developed during the 1940s. At the same time, more and more influenza viruses are emerging each year. Increases in travel and trade make it easier than ever for these viruses to spread. Our current system is not as responsive and effective as it should be.

The system is badly in need of modernization and must better capture advances in technology over the past decades. We need better testing to quickly learn of mutations and seasonable influenza viruses. We must increase our capacity to create cell based and recombinant vaccine doses instead of heavily relying on the more problematic egg-based vaccine doses.

The estimated production time for cell-based and recombinant vaccines is significantly quicker than egg-based vaccines, allowing for greater flexibility in the vaccine selection and manufacturing process.

NIH, the Biomedical Advanced Research and Development Authority, known as BARDA, and other agencies undertaking research in influenza and the flu vaccine must determine what precisely is limiting vaccine effectiveness, particularly with respect to the dangerous H3N2 seasonal flu strains. We must also better understand how to use adjuvants to boost the effectiveness of the vaccine, particularly among high-risk populations such as the elderly and the young.

We need a better contingency plan for vaccine mismatch uses whether due to antigenic drift or egg adaptation issues. The public health organizations must increase surveillance particularly in the

Southern Hemisphere so we can know as early as possible when a seasonal flu vaccine will not be as effective as we hope.

The CDC must have a more robust and effective communications strategy when dealing with the flu. In particular, healthcare professionals must be better educated about the use of antivirals instead of antibiotics when treating the flu. The CDC must also come up with a better plan to increase vaccination rates.

And finally, HHS must prioritize updating its pandemic plans some of which have not been updated for over a decade. These updates which are now not expected until sometime next year are long overdue.

I am encouraged by the work that has been done in the wake of last year's flu season, but we must also ask ourselves where we are falling short and what we need to do to modernize our response to influenza. Our Nation deserves a 21st century response to this problem.

I thank our witnesses from CDC, FDA, BARDA, and NIH, and look forward to hearing their testimony today.

[The prepared statement of Mr. Murphy follows:]

PREPARED STATEMENT OF HON. TIM MURPHY

Good morning. Earlier this year, in February, this subcommittee held a hearing on last year's flu vaccine mismatch. This mismatch to the predominant flu virus resulted in more deaths and hospitalizations because of the vaccine's lower than usual effectiveness. Today, we are returning to that issue to discuss what our public health agencies have learned in the intervening months. I want to thank the ranking member for her assistance in this important topic. We have worked closely on this issue, sending bipartisan letters and receiving briefings, not only on this year's flu vaccine, but also on our broader response to seasonal and pandemic flus.

Influenza is a leading cause of death in the United States, especially in a severe flu season. Each year, millions of Americans receive flu shots to help protect against the illness. Getting a flu shot is important—even in a bad flu season, the vaccine can reduce the symptoms and duration of the flu. I encourage everyone who has not already received a flu shot this season to get one, even if the vaccine is not perfect.

Last year, the United States experienced a severe flu vaccine mismatch. Public health officials designed the vaccine based on information available in February, but the virus mutated before the flu season began, resulting in an effectiveness rate of only 19 percent for the vaccine, and even lower for senior citizens. We have learned, however, that even in a good year, the effectiveness of the vaccine is lower than it should be. In four of the last 10 years, the flu vaccine effectiveness rates fell below 40 percent. It is clear that the seasonal flu can cause severe public health impacts on the same scale as a pandemic flu. The time for an updated approach to dealing with the flu has long passed.

The committee's oversight work has made a difference. The Department is now treating the seasonal flu as a higher priority. Tools and plans typically reserved for pandemic flu situations are being considered in the fight against the seasonal flu. An HHS influenza working group has compiled 13 issues and recommendations to improve the influenza vaccine development and manufacturing process. They are working to improve surveillance, utilize technology to speed vaccine production, and make more effective vaccines.

But there is still much work to be done. The issues surrounding the flu vaccine are not new—we are still largely manufacturing flu vaccines and detecting flu virus changes with technology developed during the 1940s. At the same time, more and more new influenza viruses are emerging each year. Increases in travel and trade make it easier than ever for these viruses to spread. Our current system is not as responsive and effective as it should be.

The system is badly in need of modernization, and must better capture advances in technology over the past decades. We need better testing to quickly learn of mutations in seasonal influenza viruses. We must increase our capacity to create cell-based and recombinant vaccine doses, instead of heavily relying on the more problematic egg-based vaccine doses. The estimated production time for cell-based

and recombinant vaccines is significantly quicker than egg-based vaccines, allowing for greater flexibility in the vaccine selection and manufacturing process.

NIH, the Biomedical Advanced Research and Development Authority (BARDA), and other agencies undertaking research into influenza and the flu vaccine must determine what precisely is limiting vaccine effectiveness, particularly with respect to the dangerous H3N2 seasonal flu strains. We must also better understand how to use adjuvants to boost the effectiveness of the vaccine, particularly among high-risk populations such as the elderly and the young.

We need a better contingency plan for vaccine mismatch issues, whether due to antigenic drift or egg adaptation issues. The public health organizations must increase surveillance, particularly in the Southern Hemisphere, so we can know as early as possible when a seasonal flu vaccine will not be as effective as we hope.

The CDC must have a more robust and effective communications strategy when dealing with the flu. In particular, health care professionals must be better educated about the use of antivirals instead of antibiotics when treating the flu. The CDC must also come up with a better plan to increase vaccination rates.

Finally, HHS must prioritize updating its pandemic plans, some of which have not been updated for over a decade. These updates—which are now not expected until sometime next year—are long overdue.

I am encouraged by the work that has been done in the wake of last year's flu season. But we must also ask ourselves where we are falling short and what we need to do to modernize our response to influenza. Our nation deserves a 21st century response to this problem.

Mr. MURPHY. And I now recognize ranking member of the subcommittee Ms. DeGette of Colorado for 5 minutes.

OPENING STATEMENT OF HON. DIANA DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Ms. DEGETTE. Thank you so much, Mr. Chairman. I really think it is so important the bipartisan work that we are doing on these flu issues. Oftentimes, people ask me what keeps me up at night and I always say having been in Congress when we had the H1N1 flu some years ago, the concept of a flu pandemic and what it could do for our country and our constituents and the world at large, it is what is keeping me up at night. And that is why I think it is important that we have a hearing every year. I am really happy we are having it this year before the flu season has started. I think it is really critical so that we can examine what—first of all, what is happening with the seasonal flu as best as we can predict, and secondly, what we are doing to prepare ourselves for better response to the seasonal flu and also more devastating potentials.

I see we have some medical professionals in the room here and I am always happy to see. It looks like you are students. My daughter is a medical student, and so she is also very interested in these issues.

Last year, I think, was a really harsh reminder that infectious disease is always around us and try as we might, we are not always 100 percent successful in treating the annual flu. Last year's flu vaccine was only moderately effective. Fortunately, it was not a severe strain, but nonetheless, it resulted in increased hospitalizations, particularly for vulnerable populations like senior citizens and young children.

During the course of the last season, in fact, CDC announced that the flu vaccine had only a 23 percent effectiveness rate which is significantly lower than we have observed in recent years. That was largely because the virus mutated in the 8 months between the vaccine strain selection and the onset of the flu season. And

that resulted in a mismatch between the strain of the virus used in the vaccine production and the one that we were actually circulating.

Still, we need to protect ourselves and last year even 23 percent was better than nothing. But Dr. Frieden reminded us last year that even a vaccine with a low effectiveness rate still protects millions of people from getting sick and we hope and I hear that some of the early indications are that it is a better match this year, but it is still kind of a crap shoot every year as to what is going to happen. And so that is why I am always happy to have these witnesses here today, some of whom who have been to this committee before, some are new, to hear about ways that we can strengthen our response for the future.

I want to ask the CDC about this flu season, but I also want to hear how we are going to respond in the event of a severe flu season and what we are doing to continue to prepare for the inevitability of some kind of a pandemic flu.

I was pleased to see that the administration put together a memorandum for the Secretary of Health and Human Services, based in part on lessons from last year's flu season. It offers several key areas where improvements could be made including better technology to quickly identify and isolate flu strains and efforts to improve vaccine manufacturing. And the plan also provides rough estimates of when certain activities can be achieved and which agencies are responsible for each goal.

But Mr. Chairman, as you pointed out, we are still relying on egg-based vaccines even though we have better—we have cellular techniques that are better. And frankly, this is the eighth hearing that we have had in the last 10 years. And I remember 10 years ago asking about the development of a new and more nimble vaccine potential and here we are again talking about this same thing.

And so I am really looking forward to hearing from the witnesses about the goals that they share and the memorandum that was issued and also where we are towards moving towards better technologies on vaccine production and what we are doing to improve all of the rest of our systems for more serious identification and prevention. The importance of a strong public health infrastructure that allows us to prepare and respond simply cannot be overstated. And we are in a good position, but I think our position could be improved. We need coordinated response capabilities, effective communication strategies, and critical investments so we can strengthen our response to all types of flu threats.

And so let me conclude by thanking the witnesses and agencies here today. All of you I know are very committed to this effort and we look forward to partnering with you in this on-going fight. And I yield back. Thank you, Mr. Chairman.

Mr. MURPHY. Thank you. I don't think we have any on our side, and, given that we are going to be voting soon, we will submit those for the record.

And Ranking Member Mr. Pallone wants to make a statement. You are recognized now for 5 minutes.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, I will try to shorten it, Mr. Chairman, in light of what you just said. I just want—obviously, it is important for many vulnerable Americans, seasonal flu can be dangerous. Older Americans, pregnant women, and young children are all at heightened risk for flu complications, hospitalization, and death. And last year, we experienced a severe flu season across the country. Hospitalizations were up. Seasonal flu remains a significant public health burden that requires considerable attention from our public health officials.

In addition, the lag time between the selection of the strains for the flu vaccine and the completion of the vaccine manufacturing process raises inherent difficulties. We can all get vaccinated.

Under the Affordable Care Act, flu and other immunizations are required to be covered by your health insurance without any copayments or coinsurance. I went and got my shot this morning in the infirmary. It was free and it is as easy as going to the pharmacy around the corner, so there are really no good reasons not to do it. An annual flu vaccination continues to be the best method for preventing flu.

Even in a year where the flu vaccine is less effective, flu shots still protect against and decrease the severity of flu-related illnesses. Unfortunately, many Americans still haven't gotten their flu shots. Even though we have made great progress, vaccination lags behind in adults, particularly in 18-to-64-year-olds. And the mismatch vaccine during the 2014–15 flu season highlights the need to improve our vaccine manufacturing process as well as our capacity to conduct surveillance and virus characterization in cooperation with our global partners.

So I just want to thank all of the witnesses for coming today.

[The prepared statement of Mr. Pallone follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Mr. Chairman, thank you for holding this hearing today. I think this is an important hearing on a topic of bipartisan concern.

While it is easy to get complacent about seasonal flu, it is important to remember that for many vulnerable Americans, seasonal flu can be dangerous and even deadly. Older Americans, pregnant women, and young children are all at heightened risk for flu complications, hospitalization, and death. Between 1976 and 2007, yearly estimates of flu-related deaths in the United States ranged from a low of about 3,000 to a high of 50,000.

Last year, we experienced a severe flu season. Across the country, hospitalizations were up. For people aged 65 and older, CDC recorded the highest hospitalization rates since they began collecting that data in 2005.

Seasonal flu remains a significant public health burden that requires considerable attention from our public health agencies. The tendency of flu viruses to change constantly results in challenges to our public health capabilities. We do not yet have the ability to predict in advance how severe a flu season will be, when it will peak, and what flu strains will dominate. There are also many things that we still don't know about why the flu vaccine is more effective in certain individuals, and how the health status of the individual may affect the body's immune response.

In addition, the lag time between the selection of the strains for the flu vaccine and the completion of the vaccine manufacturing process raises inherent difficulties. We saw this become a problem in the 2014–2015 flu season. The H3N2 virus strain that circulated during the flu season had become significantly different from the

H3N2 virus that had been used to develop the vaccine, resulting in the reduced effectiveness of the vaccine.

But here's what we do know, and what we can all do. We can all get vaccinated. Under the Affordable Care Act, flu and other immunizations are required to be covered by your health insurance without any copayments or coinsurance. I am going to get my flu shot today. It's free, and it's as easy as going to the pharmacy around the corner, so there are really no good reasons not to do it.

Annual flu vaccination continues to be the best method for preventing flu and its potentially severe complications in both children and adults. Getting the flu vaccine reduces flu-associated illness and adverse health outcomes. For instance, in the 2013–2014 flu season, vaccination prevented an estimated 7.2 million influenza-associated illnesses, 3.1 million medically attended illnesses, and 90,000 hospitalizations.

Even in a year where the flu vaccine is less effective, flu shots still protect against and decrease the severity of flu-related illnesses. Moreover, flu shots don't only protect the vaccinated. Vaccinating yourself not only increases the odds that you won't get sick this season, but also protects everyone you come in contact with, such as your older parents, or your sister's new baby.

Unfortunately, many Americans still haven't gotten their flu shots. Although we have made great progress in getting children vaccinated, particularly young children, vaccination rates lag behind in adults, particularly in 18-to-64-year-olds. I look forward to hearing from CDC about what strategies have been effective in improving vaccination rates in the past, and how we can continue to improve vaccination rates going forward.

Additionally, the mismatched vaccine during the 2014–2015 flu season highlights the need to improve our vaccine manufacturing process, as well as our capacity to conduct surveillance and virus characterization in cooperation with our global partners. I look forward to hearing from BARDA, CDC, NIH, and FDA about new technologies and initiatives to better detect emergent viruses, enhance vaccine effectiveness, and speed vaccine production.

I want to thank all the witnesses for coming today. I look forward to hearing from each of you about what your agencies are doing to improve flu surveillance, vaccine manufacturing processes, and vaccination rates.

Mr. PALLONE. If I could submit my full statement to the record, Mr. Chairman, I would ask unanimous consent to do that.

Mr. MURPHY. Without objection, we will do that. And if any other Members have an opening statement, I will ask unanimous consent the Members have those submitted without objection and will be entered into the record.

I would now like to introduce the witnesses on the panel for today's hearing. Dr. Anne Schuchat is the Principal Deputy Director for the Centers for Disease Control and Prevention. Dr. Robin Robinson is the Director of the Biomedical Advanced Research and Development Authority, otherwise known as BARDA, within the Office of the Assistant Secretary for Preparedness and Response. Dr. Carole Heilman is the Director of the Division of Microbiology and Infectious Diseases within the National Institute of Allergy and Infectious Disease, the National Institutes of Health. And Dr. Karen Midthun is the Director of the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration. We probably have about a century of education at that table. Thank you.

I will now swear in the witnesses. You are aware that the committee is holding an investigative hearing and when doing so has the practice of taking testimony under oath. Do any of you have any objections to testifying under oath?

[No response.]

Seeing none, the Chair then advises you that under the rules of the House and the rules of the committee, you are entitled to be advised by counsel. Do you desire to be advised by counsel during your testimony today?

And everybody says no. So in that case, please rise and raise your right hand. I will swear you in.

Do you swear the testimony you are about to give is the truth, the whole truth, and nothing but the truth?

All the witnesses have answered in the affirmative. You are now under oath and subject to the penalties set forth in Title 18 Section 1001 of the United States Code. We will recognize you each for a 5-minute summary of your statement. Please try and keep it on time because we are tight for votes.

Doctor, you are first.

STATEMENTS OF ANNE SCHUCHAT, M.D., PRINCIPAL DEPUTY DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; ROBIN A. ROBINSON, PH.D., DEPUTY ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE AND DIRECTOR, BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY, DEPARTMENT OF HEALTH AND HUMAN SERVICES; CAROLE A. HEILMAN, PH.D., DIRECTOR, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH; AND KAREN MIDTHUN, M.D., DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF ANNE SCHUCHAT

Dr. SCHUCHAT. Good morning, Mr. Chairman, and members of the committee. I am Dr. Anne Schuchat, Deputy Director of the Centers for Disease Control and Prevention.

I shared with the committee last February in the midst of the 2014–15 season that influenza is a formidable adversary. The propensity of influenza viruses to change presents unique challenges. New flu vaccines are made each year and updated as needed based on our best determinations of which viruses are likely to be most common during the next season. The vaccine development process is complex and time consuming with the vast majority of flu vaccines still dependent on egg-based production technology.

And while we tackle seasonal influenza, we must conduct constant global surveillance and prepare for the emergence of dramatically changed or shifted influenza viruses that could trigger the next pandemic.

The 2014–15 season was especially severe. The H3N2 influenza viruses that dominated posed substantial challenges. Even during seasons when vaccine and circulating viruses are well matched, we tend to see more severe disease when H3N2 viruses are predominant. H3N2 viruses have been becoming more difficult to grow in eggs. And last season's H3N2 viruses were difficult to characterize, using the routine lab tests that still work well for other influenza viruses.

The unique properties of H3N2 viruses also present challenges for vaccine production. Last year, we saw how devastating seasonal influenza can be. The severe season typical of H3N2 years was exacerbated by circulation of strains that had drifted away from the

H3N2 strain used for vaccine development. We saw disappointing vaccine effectiveness against these viruses. We saw the highest hospitalization rates in people 65 and older that we have seen since this type of tracking began nearly a decade ago. Despite this, the vaccine actually worked well against influenza B viruses that also circulated last season.

I will briefly mention where we are now as we head into the 2015–16 flu season, then describe the steps we have been taking to improve our efforts in light of the problems we faced last winter.

Currently, influenza circulation is low and flu season hasn't yet begun. We can't predict exactly when flu activity will start accelerating or which viruses will circulate most commonly in the weeks and months ahead. Thus far, we have seen more H3N2 viruses than H1N1 or B viruses.

Current global lab data continues to indicate that most circulating flu viruses remain similar to the reference vaccine viruses used for development of the 2015–16 U.S. vaccines. While we can't predict how effective this season's flu vaccines will be, the composition of the 2015–16 U.S. vaccine was updated from the '14-'15 one to better match circulating viruses. And global data available right now, suggests that a vaccination with Northern Hemisphere flu vaccine should offer protection against the majority of viruses.

I could speak at length about the significant improvements we have made to our influenza program over the last decade. Instead, I will describe what CDC learned from the past season and what we have done to improve our ability to rapidly detect, respond, and prevent flu.

First, we continue to work toward better detection of influenza viruses and overcome challenges in characterizing H3N2 viruses to detect important changes to them. We are implementing new testing paradigms where we perform sequencing first on all specimens received for characterization. This gives actionable data much quicker than before. We are working with domestic and international public health partners to transfer this technology to them, reducing processing time by weeks. We are developing better assays to characterize seasonal viruses and enhance our ability to identify emerging viruses. This season we are implementing right sizing virus surveillance initiative with 64 public health labs.

We have put out the call to all our international partners to increase frequency and numbers of specimens shipped to Collaborating Centers and we are trying to maintain the gains we have made in the last 10 years in our global surveillance. We are working to provide better characterized vaccine viruses to WHO and manufacturers for vaccine production We are increasing the number of viruses with the potential drift capability that are fully characterized as cell and egg propagated viruses to expand the pool of viruses available for vaccine composition decisions. And we are improving upon the vaccine virus selection process, exploring a staggered approach whereby decisions about difficult vaccine components are made closer to the season and talking to the WHO Flu Network and manufacturers about moving the decision time line as a whole closer to the season.

Although I have spoken about things we would like to do better, I want to remind you the vast progress we have made in detecting,

preventing, and responding to influenza threats over the past decade. Flu is a formidable opponent, but CDC is working 24/7 to protect Americans from this and other threats at home and abroad. And I am happy to answer questions.

[The prepared statement of Dr. Schuchat follows:]

Testimony before the
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
United States House of Representatives

U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?

Anne Schuchat, MD (RADM, USPHS)
Principal Deputy Director, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

CDC
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For Release upon Delivery
Thursday, November 19, 2015
Expected at 10:00 a.m.

Introduction

Good morning Chairman Murphy, Ranking Member DeGette, and Members of the Subcommittee. I am Dr. Anne Schuchat, Principal Deputy Director of the Centers for Disease Control and Prevention (CDC). We thank the Committee for its continued interest in seasonal influenza. Seasonal influenza is a serious public health problem. As I discussed with you last February, the 2014-2015 season underscored that this respiratory illness should not be characterized as "just the flu." Our concerns about seasonal and pandemic influenza keep many of us in public health awake at night as time and again, this virus is a worthy adversary to our best science. I look forward to discussing with you today ways in which we are working with our partners to continue to improve influenza prevention and control.

Influenza is unpredictable because flu viruses are constantly changing. Each flu season, different flu viruses can spread, and can affect people differently based on their individual immune systems. We cannot say in advance of a season how severe it will be, which viruses will predominate, or who will be most affected. Between five percent and 20 percent of Americans are sickened by the virus annually – hundreds of thousands of those who fall ill with the disease end up hospitalized and thousands or tens of thousands die from influenza-related illness.[1] Looking at three decades of data from 1976 to 2007, we estimate that flu deaths in the United States during any one season have ranged from about 3,000 to 50,000 Americans[2]. Direct medical costs for influenza are estimated to exceed $10 billion each year in the U.S., with more than $80 billion indirect costs[3].

Despite everything that we cannot predict about influenza viruses, the single best thing you can do to protect yourself and your family from influenza is to get vaccinated. For the last decade, CDC has supported studies to determine the effectiveness of flu vaccines. Results have shown that the effectiveness of the vaccine varies. When most circulating flu viruses are similar to the viruses used to develop vaccine, vaccination can

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[1] Influenza-Associated Hospitalizations in the United States 1979 Through the 2000-2001 Respiratory Seasons ." *Journal of American Medical Association's* September 14, 2004 issue (volume 292, no. 11).
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reduce the risk of flu illness by 50 percent to 60 percent. But vaccine effectiveness can be lower in certain people, or against viruses that have changed, or "drifted" from the vaccine viruses used to develop vaccine as we saw last season with H3N2 viruses, which had become significantly different or "drifted from" the H3N2 virus used to develop vaccine. While these studies show the need for continued progress toward making better flu vaccines, they also help us to see the impact that vaccines have each year. Studies show flu vaccine helps prevent illnesses. It helps prevents medical visits for flu-related illness. It helps prevents hospitalizations. It helps protect a pregnant woman from influenza. Flu vaccine is a valuable public health tool, yet only about half of Americans get vaccinated each year.

While flu vaccine is the best way to prevent influenza illness and protect against its potentially deadly consequences, if a person becomes sick with flu antiviral flu drugs are a treatment option. Since 1999 a large and growing body of observational data, including in hospitalized patients, shows there are benefits to using antiviral drugs beyond the treatment of uncomplicated illness. In medical practice, these drugs have been documented to reduce serious flu complications. In 2008, CDC began recommending these drugs for early treatment of severely ill and high risk patients based on that data. During and after the 2009 H1N1 pandemic, clinical studies in medical practices continued to show that people very ill with flu who got antiviral drugs fared better than those who did not; sometimes these drugs were associated with preventing severe illness and death. For that reason, CDC continues to recommend that the neuraminidase inhibitor influenza antiviral drugs be used for early treatment of people who are very sick with influenza or of people who are sick who are at high risk of serious influenza-associated complications. Most previously healthy people will recover from flu without treatment.

CDC's recommendations for using influenza antiviral medications aim to protect the people who are most vulnerable to serious complications from flu. The recommendations for antiviral drugs are based on data from randomized clinical trials as well as from observational studies of patients receiving treatment in medical

practice. CDC recognizes that currently recommended influenza antiviral drugs have limitations; however, these drugs are the only influenza-specific therapy approved by FDA with activity against circulating influenza viruses.

Influenza viruses are constantly changing; therefore, unlike other vaccines, annual immunization with seasonal influenza vaccine is recommended. There are two types of changes we continually monitor for in influenza viruses. "Antigenic shift" Is an abrupt, major change in influenza A viruses, resulting in a new influenza A subtype that is so different from circulating human flu viruses that most people do not have immunity to the new (e.g. novel) virus. "Antigenic drift" refers to small changes in the genes of influenza viruses that happen continually as the viruses spread and infect people. These small genetic changes can accumulate over time. This results in the emergence of viruses that are sufficiently different antigenically from previously circulating viruses. When this happens, the body's immune system may not recognize those viruses. Because of antigenic drift, twice a year the World Health Organization (WHO) convenes a consultation with the Directors of WHO Collaborating Centers and representatives of key national laboratories. They review the results of surveillance, laboratory and clinical studies, and the availability of vaccine viruses, and make recommendations on the composition of the influenza vaccine. These meetings take place in February for selection of the upcoming Northern Hemisphere's seasonal influenza vaccine and in September for the Southern Hemisphere's vaccine. WHO recommends specific vaccine viruses for inclusion in influenza vaccines, but then each individual country makes their own decision about which viruses should be included in influenza vaccines licensed in their country. In the United States, the Food and Drug Administration (FDA) makes the final decision about vaccine viruses for influenza vaccines sold in the United States.

2014-2015 and 2015-16 Influenza Seasons

H3N2 viruses were the most predominant by far last season. In the past, H3N2 seasons have been associated with more illnesses and deaths in certain populations in relation to H1N1-predominant seasons. The

2014-2015 season was severe for the elderly in particular. We saw the highest hospitalization rates ever documented since this type of record-keeping began (in 2005-06) among people 65 and older, while hospitalization rates in other age groups were within the range seen in other H3N2-dominant years. Exacerbating the situation last season was the fact that most of the H3N2 viruses that circulated in the United States last season had changed, or "drifted," from the viruses which had circulated during the prior season and which had been selected to develop the 2014-15 Northern Hemisphere seasonal flu vaccines. This resulted in reduced vaccine effectiveness against circulating H3N2 viruses last season, which in turn caused greater susceptibility to infection among vaccinated persons, particularly older adults. The drifted H3N2 viruses are difficult to characterize using traditional antigenicity tests and are difficult to grow in eggs. This makes surveillance more difficult, and it also make creating a candidate vaccine virus more difficult. Most of the vaccine supply manufactured for the United States continues to rely on egg-based technology.

Currently, influenza circulation is low, and the 2015-2016 influenza season has not begun. The most recent CDC FluView report indicated that flu activity in the United States remains low. CDC has received reports of early institutional outbreaks of flu. In the United States, flu outbreaks can happen as early as October and can last as late as May. The flu season is said to have begun when certain key flu indicators (for example, levels of influenza-like illness [ILI], hospitalization and deaths) rise and remain elevated for a number of consecutive weeks. Usually ILI increases first, followed by an increase in hospitalizations, which is then followed by increases in flu-associated deaths. We cannot predict exactly when this threshold will be crossed or which viruses will circulate most widely in the coming months; we have seen a predominance of H3N2 viruses in surveillance.

2015-16 Vaccine

While we cannot predict how effective this season's influenza vaccines will be, the composition of this season's vaccine has been updated to better match circulating viruses. Both the influenza A H3N2 and influenza B components in the 2015-16 vaccine were updated from the 2014-15 formulation. While we wait to gather and analyze epidemiologic information and to conduct field studies of vaccine effectiveness, laboratory data can give some indication of how well the vaccine might work. Current global laboratory data indicate that most

circulating influenza viruses are similar to the reference vaccine viruses used for development of the 2015-2016 U.S. vaccines. These data suggest that vaccination with Northern Hemisphere influenza vaccine should offer protection against the majority of circulating viruses. CDC will continue to carefully review results of laboratory studies of currently circulating viruses to look for evidence that viruses are changing. We are committed to ongoing, transparent communication about the characteristics of seasonal influenza viruses and vaccine effectiveness. Our weekly interactive influenza surveillance report appears each Friday on the CDC website (http://www.cdc.gov/flu/weekly/).

Last Spring, manufacturers projected that between 171 million and 179 million doses of flu vaccine would be supplied to the U.S. market this season. While early supply projections can differ from the actual number of vaccine doses distributed at the end of the season, manufacturers report having shipped more than 123.7 million doses of flu vaccine as of October 30, 2015, a figure similar to what had been distributed by this time last season. Some manufacturers have reported shipping delays of certain vaccine formulations; however, overall, we are not aware of vaccine shortage issues at this time.

Next Steps

We appreciate the opportunity to talk with you about how we are working with HHS colleagues to better prevent influenza through more effective vaccines. CDC has a lead role in several improvement initiatives that have been identified within HHS. Particularly, we are working to improve global surveillance and virus characterization to detect emergent viruses more quickly and use this information to inform vaccine virus selection. Globally-coordinated surveillance is the foundation of the influenza vaccine virus development and selection process. It is important to ensure that the best available technologies are being used to analyze influenza viruses and likewise that the best technologies are employed in the production of influenza vaccines. The World Health Organization (WHO) Global Influenza Virus Surveillance and Response System (GISRS) is a global network that provides year-round surveillance of human and animal influenza viruses, makes recommendations on the composition of seasonal influenza vaccines, and provides candidate vaccine viruses for manufacturers to use in the production of seasonal influenza vaccines. GISRS works closely with vaccine

manufacturers through the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to provide regular updates on virus characterization, including the emergence of drifted virus that may warrant changes in vaccine formulation and the availability of new candidate vaccine viruses. CDC has served as a WHO Collaborating Center (CC) for Surveillance, Epidemiology, and Control of Influenza since 1956. CDC's Influenza Division is currently the largest global resource and reference center supporting public health interventions to control and prevent seasonal and pandemic influenza. CDC is always working to strengthen its ability to conduct epidemiologic and virologic surveillance. We are expanding the use of new technologies - including Advanced Molecular Detection –to better identify and characterize influenza viruses, as well as optimizing antigenic characterization assays. CDC also is in the process of restructuring laboratory processes to first characterize incoming virus samples using high-throughput nucleotide gene sequencing, affording a quicker and more comprehensive picture of circulating viruses and what changes they may have acquired so that we can better foresee newly emerging drifted viruses for vaccine virus development. Over a 10 year period -- in large part due to CDC'S capacity building efforts in low and middle income countries through cooperative agreements bilaterally and with all WHO Regional offices -- we have increased the numbers of countries that submit samples to the GISRS to inform vaccine strain selection process from 66 countries in 2004 to 107 countries submitting into the system in 2014. During this same period, the actual numbers of virus submissions to GISRS has increased from approximately 9,000 to almost 15,000 per year. Despite major advances made by CDC and its partners in building GISRS during the last decade, surveillance gaps remain. Expansion of GISRS through capacity building remains a CDC priority. It is critical for us to continue to support bilateral cooperative agreement partners around the world to maintain and build upon gains in global influenza surveillance and laboratory capacity.

CDC also is working to develop U.S. laboratory networks to generate and share whole influenza virus genome data. In addition, CDC is collaborating with other HHS partners to incorporate technological improvement to enhance and speed vaccine production. The improvements I've just mentioned are ones we're

making right now – we look forward to being part of the push toward the development of a universal influenza vaccine with our colleagues across the department.

Conclusion

Unlike other vaccine preventable pathogens, influenza viruses are constantly changing. The investments made by the U.S. government for the diagnosis, prevention, and control of influenza have led to increased domestic and global viral surveillance, an increase in knowledge about how the flu virus works, more choices of vaccine types, increases in the number of cases averted due to vaccination, expanded recommendations of influenza vaccination to all age groups (above the age of six months) and increased use of influenza vaccine among children and pregnant women. Although many gains in seasonal and pandemic influenza preparedness and control have been made over the years, continued improvements are needed. We will work, along with our government colleagues, academic, and industry partners, to improve use of antiviral treatment, to make more effective influenza vaccines, and to speed production of existing vaccines for all Americans.

Thank you for the opportunity to talk about CDC's role in the 2015-2016 influenza season. I am happy to answer any questions you may have.

Mr. MURPHY. Thank you. Dr. Robinson, you are recognized for 5 minutes.

STATEMENT OF ROBIN A. ROBINSON

Dr. ROBINSON. Good morning, Chairman Murphy, Ranking Member DeGette, oh sorry. Good morning. And I would recognize the chairman, Ranking Member DeGette, and the distinguished members of the subcommittee. Thank you for the opportunity to speak with you again today.

I am Dr. Robin Robinson, the Director of the Biomedical Advanced Research and Development Authority or BARDA, and the Deputy Assistant Secretary to the Assistant Secretary for Preparedness and Response or ASPR, as well as a former developer of influenza vaccines in industry.

ASPR is charged with coordinating Federal public health and medical preparedness and response to public health emergencies, providing integrating public policy and strategic direction over the national response framework, and through BARDA oversees advanced research and development and procurement of novel and innovative medical counter measures such as vaccines, therapeutics, diagnostics, and medical devices for the entire Nation to address medical consequences of manmade and naturally occurring threats like the 2009 H1N1 pandemic, the 2013 H7N9 influenza outbreak, and the recent bola epidemic.

We have funded and successfully managed the advanced development of more than 80 medical countermeasures for pandemic influenza and 18 receiving FDA approval and licensure since 2007 and 6 in the last 3 years. Additionally, we developed and procured vaccines and antivirals used in the 2009 H1N1 pandemic and stockpiled vaccines that were prepared against H5N1 and H7N9 viruses.

Through partnerships with NIH, CDC, FDA, industry, and academia, we have met and overcome many, but not all, of the challenges inherent to making vaccines for seasonal and pandemic influenza. These achievements include first modernization of influenza vaccines through the development and licensure of new cell- and recombinant-based influenza vaccines and antigen-sparing adjuvanted vaccines; second, shortening pandemic influenza vaccine manufacturing time lines through advancements such as synthetic biology and new vaccine potency assays; third, establishment and maintenance of pre-pandemic influenza vaccine stockpiles for H5N1 and H7N9 viruses; fourth, multi-fold expansion of domestic pandemic influenza vaccine production to meet U.S. pandemic vaccine needs; and lastly, providing emergency response capabilities to develop, manufacture, and test new pandemic influenza vaccines through our national medical countermeasure response infrastructure.

Despite these significant accomplishments, our influenza vaccine preparedness work is not over. Incremental progress towards more effective influenza vaccines has been noted in recent years, but much more is needed. Going forward, there is reason for hope, that more effective influenza vaccines may be within our grasp. The discovery of new influenza viral targets, novel adjuvants, and heterotypic prime/boost vaccine strategies may afford more durable

and broader immunity and spark renewed interest and efforts to develop more effective influenza vaccines with universal potential.

With the National Institute of Allergy and Infectious Disease, we are supporting the development of several new influenza vaccine candidates that may be more effective against a wider range of influenza viruses and that may serve both seasonal and pandemic influenza needs. Additionally, the National Institute of Allergy and Infectious Disease and we are supporting new methods to help forecast the select seasonal and pandemic influenza vaccine strains based on evolutionary biology technologies.

With our HHS partners, we are bringing a number of our advancements in pandemic influenza vaccines to address virus antigenic drift and seasonal influenza vaccine mismatch issues. These actions include better virus surveillance and characterization, new seasonal virus risk assessment tools, faster preparations of better candidate vaccine viruses, faster potency assays and reagent lot variation and more effective influenza vaccines.

Beyond the successes that we have achieve domestically, improved global coordination is critical. We have engaged our global partners and industry several times this year on our improvement efforts for seasonal influenza vaccines. Recently, we evaluated several of these actions in a tabletop exercise with HHS agencies, WHO, representatives from other countries, and vaccine manufacturers. The exercise showed that several of these mitigation measures may improve the way that we prepare candidate vaccine strains and make seasonal influenza vaccines.

In addition, the exercise provided improved framework on how the U.S. and global partners may manage viral antigenic drift and vaccine mismatches better.

In conclusion, influenza viruses that may cause seasonal epidemics and potential pandemics continue to evolve and change, infect animals and man and pose significant threats to global and domestic public health. Last year's limited seasonal influenza vaccine effectiveness and this year's arrival of H5 avian influenza viruses in U.S. poultry underscore our urgent and compelling need to complete the mission.

To be better prepared, our Nation must continue to invest in domestic seasonal and pandemic preparedness and work with key global partners. Thank you for your generosity and I look forward to your questions.

[The prepared statement of Dr. Robinson follows:]

Written Testimony
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
United States House of Representatives

"The U.S. Public Health Response to Seasonal Influenza"

Statement of

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Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

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Introduction

Good morning Chairman Murphy, Ranking Member DeGette, and distinguished Members of the Subcommittee. Thank you for providing me the opportunity to speak with you today in regard to medical countermeasure (MCM) preparedness and response efforts for seasonal and pandemic influenza. I am Dr. Robin Robinson, Director of the Biomedical Advanced Research and Development Authority (BARDA) and Deputy Assistant Secretary to the Assistant Secretary for Preparedness and Response (ASPR) at the Department of Health and Human Services (HHS). I look forward to talking with you about our advancements in pandemic influenza vaccine preparedness and their positive influence on seasonal influenza vaccines.

Recognizing lessons learned from disasters including the terrorist attacks on 9/11, the anthrax attacks in 2001, and Hurricane Katrina, ASPR was established in 2006 to improve coordination and direction across the spectrum of HHS preparedness and response activities. Under the Public Health Service Act, as amended by the Pandemic and All-Hazards Preparedness Act (PAHPA) and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), ASPR was established as the lead for HHS emergency preparedness and response and serves as the principal advisor to the Secretary regarding Federal public health and medical preparedness and response to public health emergencies. ASPR's responsibilities are broad and include: overseeing advanced research, development, and procurement of resulting medical countermeasures; coordinating with health care systems; and providing integrated policy and strategic direction under the National Response Framework. In addition, ASPR directs medical and public health grants and cooperative agreements, provides leadership in international programs and policies with global impact, and has developed and submitted a five-year budget

plan for countermeasure priorities. ASPR oversees the National Disaster Medical System (NDMS), the Hospital Preparedness Cooperative Agreement Program (HPP), and BARDA. Moreover, through guidance documents like the National Health Security Strategy (NHSS) and Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan (SIP), ASPR leads the path forward for our partners and stakeholders.

Within ASPR, BARDA is the agency mandated to support advanced research and development and procurement of novel and innovative MCMs such as vaccines, therapeutics, antiviral and antimicrobial drugs, diagnostics, and medical devices to address the medical consequences of man-made chemical, biological, radiological, and nuclear (CBRN) agents of terrorism and naturally-occurring threats. Recent infectious disease threats that BARDA has responded include the 2009 H1N1 pandemic, the 2013 H7N9 influenza outbreak, the 2014-2015 Ebola epidemic, and current MERS-CoV endemic outbreaks.

By supporting advanced research and development of MCM candidates, BARDA addresses the medical consequences of threats and bridges the gap between early research and development and advanced development towards Food and Drug Administration (FDA) approval and potential procurement of these MCMs. Advanced development includes the critical steps necessary to transform an MCM candidate into a product that is ready to use. Since 2006, we have funded and successfully managed the advanced development of nearly 200 MCMs for CBRN threats, pandemic influenza, and emerging infectious diseases. Twenty two of these products have received FDA approval since 2007. We have also made available or stockpiled

twelve CBRN medical countermeasures under Project BioShield and 18 influenza medical countermeasures for the 2009 H1N1 and avian influenza H5N1 and H7N9 outbreaks.

Seasonal influenza epidemics occur every year. However, periodically a novel influenza virus strain, for which there is little human immunity, will emerge and cause a global pandemic like the 2009 H1N1 pandemic, or worse, the pandemic of 1918. Because influenza viruses mutate as they traffic and reassort primarily among birds, swine, and humans, achieving protection against seasonal influenza viruses is a significant challenge. Means to control and address the medical and public health consequences of influenza include social distancing, proper hygiene practices, vaccination, antiviral drugs, and diagnostics. In the last decade, we have been repeatedly reminded about the complexity of managing seasonal and pandemic influenza both globally and nationally. The most recent examples include the seasonal influenza vaccine mismatch to the antigenically-drifted H3N2 virus during the 2014-2015 influenza season and the avian influenza H5 viruses that killed millions of domestic birds in the Midwest earlier this year.

The potential of the H5N1 virus to become a severe influenza pandemic resembling the 1918 pandemic led to the issuance and implementation of the *National Strategy for Pandemic Influenza* (2005) and sparked important efforts to develop new influenza medical countermeasures, establish vaccine and antiviral drug stockpiles, and expand domestic vaccine manufacturing. Lessons learned from the H1N1 pandemic resulted in the President's Council of Advisors on Science and Technology's (PCAST's) *Report to the President on Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza* (2010), which recommended improvements in virus surveillance, in vaccine research and development,

and in influenza vaccine manufacturing. As a call to action, HHS reviewed and revised existing plans to develop new influenza vaccines, antiviral drugs, and diagnostics to assess the size, composition, and usage of influenza vaccine and antiviral drug stockpiles, and to expand our domestic influenza vaccine manufacturing infrastructure and capacity. The common thread throughout these preparedness and response plans was that seasonal and pandemic influenza are inextricably interwoven; what we do in one area directly affects what we do in the other. Ten years after the HHS Pandemic Plan (2005) was issued, HHS is working to update the HHS Pandemic Plan based on our experiences with the 2009 H1N1 pandemic, the continual emergence of new avian influenza viruses with pandemic potential, and advancements we have made towards making more and better influenza vaccine sooner.

HHS, with its integrated and coordinated Federal agencies - the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Office of the Assistant Secretary for Health (OASH), FDA, and ASPR including BARDA - have partnered with industry, other governments, and academia to address these seasonal and pandemic influenza challenges. ASPR coordinates overall HHS and Government-wide influenza pandemic preparedness and response strategies and action plans in concert with seasonal influenza activities managed out of the National Vaccine Program Office in OASH. Within ASPR, BARDA is directly responsible for working with industry, academia, other governments, and Federal partners to: (i) support advanced development of new influenza vaccines, antiviral drugs, and diagnostic devices leading to FDA approval for the U.S. market; (ii) improve influenza vaccine manufacturing resulting in greater vaccine production yields and availability sooner; (iii) build and maintain stockpiles of pre-pandemic influenza vaccines for the critical

workforce and antiviral drugs at the Federal and State levels; and (iv) expand domestic and global pandemic influenza vaccine manufacturing infrastructure and capacity multifold. While the recent introduction of quadrivalent, high-dose, and novel seasonal influenza vaccines by vaccine manufacturers represents incremental progress towards more effective influenza vaccines, there remain significant technical challenges before a substantially more effective influenza vaccine is available. The discovery of new viral targets within the last four years has renewed interest and efforts to develop the long-sought-after "universal" influenza vaccine.

Because of the close scientific and technical connections between seasonal and pandemic influenza, developing better influenza vaccines is a top priority for ASPR. Our work to develop better influenza vaccines, including methods based on the field of evolutionary biology, may augment existing methods to forecast and select new seasonal and pandemic influenza vaccine strains. In parallel, we launched an initiative to support advanced development of more effective influenza vaccines that may elicit greater and broader immunity for all populations, longer duration of immunity, and greater cross-protection against influenza virus variants, and that may serve as primers for pandemic influenza vaccines. To accomplish our goal of developing better influenza medical countermeasures, we added immunotherapeutics or antibodies to our antiviral drug portfolio as a new approach to treat severe cases of influenza.

ASPR Accomplishments in Influenza Vaccines

Since December 2005, HHS has been supporting medical countermeasures for seasonal and pandemic preparedness activities. Following the release of the Department's 2010 *PHEMCE Review* and the aforementioned PCAST report (2010), HHS made adjustments and took steps to

execute the pandemic influenza preparedness priorities enumerated in the review and report. HHS has made significant progress improving vaccines and manufacturing technologies. Specifically, we have partnered with industry to achieve the following:

- Modernization of influenza vaccine manufacturing systems through the development and licensure of new cell- and recombinant-based influenza vaccines as well as antigen-sparing vaccines
    - Flucelvax (2012), the first cell-based seasonal influenza vaccine in the United States
    - Flublok (2013), the first recombinant-based seasonal influenza vaccine in the United States
    - Q-Pan H5N1 vaccine (2013), the first adjuvanted pandemic influenza vaccine in the United States
    - Fluad seasonal influenza vaccine (2015), recommended by the recent VRBPAC for licensure as an adjuvanted seasonal influenza vaccine for seniors in the United States;
- With NIH, CDC, and FDA, we launched the Influenza Vaccine Manufacturing Improvement (IVMI) initiative, as recommended by PCAST to optimize the generation of high yielding vaccine seed strains and alternative potency and sterility assays, to expedite influenza vaccine availability. The IVMI initiative improvements may cut weeks off the vaccine manufacturing process and increased production yields;
- Establishment and maintenance of pre-pandemic influenza vaccine stockpiles for H5N1 and H7N9 viruses with pandemic potential to rapidly immunize the critical workforce at

the onset of an influenza pandemic. In parallel, ASPR and CDC developed and implemented the Influenza Risk Assessment Tool (IRAT) in 2010 to inform the composition and prioritization of vaccines in this stockpile;

- Multi-fold expansion of domestic influenza vaccine production for pandemic preparedness by retrofitting older manufacturing plants (2007-2011) and building new state-of-the art, award-winning manufacturing facilities (2009-2012) through a public-private partnerships with industry;
- Establishment of a national infrastructure to rapidly develop, manufacture, and test new influenza vaccines and medical countermeasures for emerging infectious diseases, such as Ebola. This infrastructure responded in 2013 with the development, production, testing, and stockpiling of H7N9 influenza vaccines and more recently Ebola vaccine and monoclonal antibody therapeutic candidates in 2014-2015; and
- Establishment of a global vaccine manufacturing infrastructure with the World Health Organization (WHO) in 2006 in eleven (11) developing countries to make pandemic influenza vaccines and vaccines for other diseases. This initiative has resulted in the establishment of manufacturing facilities making four licensed influenza vaccines with a current capacity to produce 300 million doses of pandemic influenza vaccine.

HHS Influenza Improvements in Action – Seasonal Influenza Vaccines (2015)

HHS responded to the H3N2 antigenic drift and seasonal influenza vaccine mismatch in 2014-2015 by tasking the Department's senior influenza leaders and experts last winter to provide a comprehensive set of recommendations to the HHS Secretary on how to address the issue of vaccine mismatch in the near and long term. HHS convened numerous meetings from December

2014 through May 2015 with internal and external influenza and vaccine experts from government, industry, and academia to understand the complexities of virus antigenic drift, vaccine mismatch, and influenza vaccine manufacturing and how seasonal vaccines and their manufacturing may be changed to accommodate this type of virus variance. In May 2015, senior HHS influenza leaders provided a set of twenty (20) recommendations to HHS leadership that may improve virus surveillance and characterization, vaccine design, vaccine manufacturing, vaccine availability and distribution, and ultimately vaccine effectiveness. In June 2015, ASPR hosted a meeting with the influenza vaccine manufacturers constituting the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and with representatives from the WHO, the government of the United Kingdom, HHS agencies, and others to review current influenza epidemiology. This review was relative to the current seasonal influenza vaccine, the HHS recommendations for improving responses to seasonal influenza vaccine mismatches, an exercise scenario similar to the 2014-2015 seasonal influenza antigenic drift and vaccine mismatch, and the current timelines for production of a new seasonal influenza vaccine and what improvements could be made to reduce those timelines.

From these recommendations and exchanges with U.S. and international public and private stakeholders, HHS developed an action plan to address vaccine mismatch for seasonal influenza. Many of these recommended actions stemmed from ongoing pandemic influenza preparedness activities such as the IVMI initiative and universal influenza vaccine development. Several of these seasonal influenza vaccine improvement actions are being implemented over the next year. One already in place involves earlier and more frequent communication on antigenic changes in circulating influenza viruses during the year from CDC to senior leaders at HHS, FDA, WHO,

vaccine manufacturers, and between FDA and the Chair of VRBPAC. Several advances derived from pandemic influenza vaccine preparedness are being transitioned by CDC and FDA into the development of seasonal candidate vaccine viruses and seasonal vaccine potency reagents with vaccine manufacturers. Implementation of the other action items is also underway to reach intermediate and long term goals. Many of the immediate actions were evaluated in a recent exercise with HHS agencies, WHO, representatives from other countries, and vaccine manufacturers. The exercise was expected to indicate whether these recommended actions would have a significant impact on improving seasonal influenza vaccines. In addition, the exercise was expected to show how the United States, WHO, other countries, and vaccine manufacturers could manage virus antigenic drift and vaccine mismatches better.

The Future of Influenza Vaccines

ASPR is working with NIH to foster collaborations with academia and industry in pursuit of more effective influenza vaccines. New evolutionary biology methods such as antigen cartography may be able to predict influenza virus evolution better and understand immune responses to the influenza viral hemagglutinin (HA) proteins from genetically-distinct viruses better. By generating specific and random influenza virus mutants to seasonal and pandemic influenza viruses, the evolutionary trend for new virus strains may be understood better and thus may inform vaccine strain selection. With these results, future vaccine candidates may be designed using this forward-looking information and may provide more effective vaccines through what is called "back-boost" vaccine immunity. We are also supporting such studies to inform the composition of pre-pandemic vaccine stockpiles, as well as seasonal human vaccine strains.

The 2010-2011 discovery that the conserved regions on the stalk of the influenza hemagglutinin protein, which is the major immunogenic component of influenza vaccines, could elicit protective immunity across many influenza virus strains has brought renewed interest into the development of new types of influenza vaccines or so-called "universal influenza vaccines" and monoclonal antibodies as new immunotherapeutics. Several current vaccine candidates including a chimeric HA stalk vaccine candidate are in early development supported jointly by BARDA and the NIH's National Institute of Allergy and Infectious Diseases (NIAID). This year we launched a new advanced development program for more effective influenza vaccines with universal potential and awarded one contract in September 2015 to support development of a novel influenza vaccine candidate.

Conclusion

Influenza and other emerging infectious diseases with pandemic potential continue to mutate, evolve, and infect animals and humans, posing significant threats to global public health and to the United States. Together with our Federal and industry partners, ASPR has made great strides towards pandemic influenza preparedness. While we have made progress in leveraging the improvements achieved for pandemic influenza vaccine manufacturing to benefit our seasonal vaccine needs, overall success in improving season readiness is dependent on the introduction and implementation of new technologies and new vaccines through the engagement and coordination of all stakeholders and partners including government, surveillance systems, industry, the World Health Organization and others. Last year's limited seasonal influenza vaccine effectiveness and the arrival of the avian influenza H5 viruses in the Midwest highlight

our urgent need to prioritize the necessary resources to make better seasonal and pandemic influenza vaccines. ASPR is prepared to meet those challenges and provide resources, expertise, and technical assistance for these and other promising investigational vaccine candidates.

Mr. MURPHY. Thank you. Dr. Heilman, you are recognized for 5 minutes.

STATEMENT OF CAROLE A. HEILMAN

Dr. HEILMAN. Mr. Chairman, Ranking Member DeGette, and members of the subcommittee, thank you for the invitation to discuss the National Institutes of Health's (NIH) response to the public health threat posed by influenza. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead NIH institute for research on immunologic, allergic, and infectious diseases, including influenza.

The NIAID mission balances research addressing current medical challenges with the capacity to respond rapidly to new threats from emerging and re-emerging infectious diseases, including seasonal and pandemic influenza. Given the morbidity and mortality of influenza in the United States every year, and the disease's economic burden, there remains a concerted U.S. interagency and international effort to study the global emergence and spread of novel influenza viruses to ensure that we are prepared not only for the coming flu season, but also for strains with pandemic potential.

As part of this response, NIAID's long-standing influenza research program spans basic translational and clinical research and includes efforts to develop a universal influenza vaccine that could provide durable protection against a variety of seasonal and pandemic influenza viruses.

Important to NIAID's effort are on-going collaborations with academia, biotechnology, and pharmaceutical industries and other Federal partners, particularly, CDC, FDA, ASPR, and BARDA.

NIAID's basic research on influenza focuses on understanding how influenza virus strains, including those with potential pandemic potential, evolve and causes illness in animals and humans. Many of the ways NIAID contributes fundamental knowledge about influenza is through our Centers of Excellence for Influenza Research and Surveillance Program which studies the global emergency and spread of novel influenza viruses and provides critical information to the World Health Organization.

NIAID also is using bioinformatic approaches to learn more about how influenza changes over time and how it can be prepared to rapidly respond to these changes. For example, NIAID is supporting the development of antigenic cartography, a computational method to understand evolutionary changes to influenza. This method is now being applied to data from WHO Collaborating Centers to help provide information relevant to the strain composition of the annual seasonal influenza vaccine.

In addition, an NIAID supported computational method, known as antibody landscaping, has enabled scientists to visualize how the human immune system responds to a lifetime of influenza infections. This technique is also being employed to design antigenically advanced vaccines that may allow us to vaccinate against influenza strains that have not get emerged.

To help diagnose and promptly treat influenza, NIAID supports the development of diagnostic tools that examine the molecular makeup of influenza viruses to quickly distinguish between seasonal strains and those with pandemic potential. NIAID is also

supporting development of clinical assays to determine influenza's sensitivity to neuraminidase inhibitors, drugs that can lessen the severity and duration of influenza and potentially prevent influenza in close contacts of patient.

NIAID is also responding to the emergency of antiviral resistance influenza strains by exploring new and better treatment options including broad spectrum antiviral drugs, RNA polymerase inhibitors and peptide inhibitors.

As we all know, annual influenza vaccination is the primary method to prevent seasonal influenza. Because influenza viruses evolve as they spread from person to person, the strains used in the influenza vaccine must be reevaluated every year. While recent analysis suggests that strains in the current seasonal influenza vaccine match the current circulating influenza strains, the mismatch experienced during 2014 and '15 flu season underscores the importance of NIAID's sustained support for influenza research and in particular, work towards a more broadly cross-protective or universal influenza vaccine that could generate long-lasting protection against influenza strains over multiple seasons and enhance pandemic preparedness.

NIAID research on universal vaccine is focused on several concepts, but the common principle behind each of these concepts is to identify those parts of the influenza viruses that are similar across multiple influenza strains and then maximize the immune system's potential to respond to them.

In addition to the efforts of NIAID scientists, the Institute in collaboration with BARDA is supporting a development of several potential promising universal influenza candidates by industry and academic partners. Although we cannot predict when a universal influenza vaccine will be publicly available, NIAID's lead effort has generated encouraging progress towards this goal. It is important to note that we develop universal influenza vaccines, promising candidates will need to be evaluated over several influenza seasons to determine the extent and durability of their protection.

NIAID is also helping to address scientific challenges in influenza virus reduction and NIAID is supporting efforts to create a flexible vaccine manufacturing process for seasonal pandemic influenza vaccine development including modern molecular biological techniques to help increase production efficiency and shorten manufacturing time.NIAID will continue to focus on advancing new tools to prevent and combat seasonal pandemic influenza in collaboration with academic, the biotechnology institutes, and pharmaceutical industries and other Federal partners.

Thank you for the opportunity to provide this overview of NIAID's influenza research program. I would be pleased to answer any subcommittee questions.

[The prepared statement of Dr. Heilman follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases Research Addressing the Public Health Threat of Influenza

Testimony before the

House Committee on Energy and Commerce

Subcommittee on Oversight and Investigations

Carole A. Heilman, Ph.D.

Director of the Division of Microbiology and Infectious Diseases

National Institute of Allergy and Infectious Diseases

November 19, 2015

Mr. Chairman, Ranking Member DeGette, and members of the Subcommittee, thank you for the invitation to discuss the National Institutes of Health's (NIH) response to the public health threat posed by influenza. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead NIH institute for research on immunologic, allergic, and infectious diseases, including influenza.

The NIAID mission balances basic, translational, and clinical research addressing current biomedical challenges with the capacity to rapidly respond to new threats from emerging and re-emerging infectious diseases, including seasonal and pandemic influenza. Given the morbidity and mortality of influenza in the United States every year, and the disease's economic burden, we recognize the importance of research to develop new tools to diagnose, treat, and prevent seasonal influenza, as well as prepare for the next influenza pandemic. NIAID's longstanding influenza research program includes efforts to develop a universal influenza vaccine that could provide durable protection against a variety of seasonal and pandemic influenza viruses. Important to these NIAID efforts are ongoing collaborations with academia, the biotechnology and pharmaceutical industries, and other Federal partners, particularly the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA), and the National Vaccine Program Office within the Department of Health and Human Services.

Basic Research

NIAID support for basic research on influenza continues to inform the development of new and improved vaccines, diagnostic tools, and antiviral drugs applicable to both seasonal and pandemic influenza strains. As part of this focus, NIAID supports fundamental research to better

understand the evolution and pathogenesis of influenza viruses in animals and humans. Researchers supported by NIAID's Centers of Excellence for Influenza Research and Surveillance (CEIRS) program are studying the global emergence and spread of novel influenza viruses, critical information that is provided to the World Health Organization (WHO). Influenza virus surveillance and sequencing using next-generation genomic technologies supported by NIH have begun to provide a more detailed picture of the evolution of the influenza virus and insights into controlling the impact of influenza outbreaks. Additionally, further understanding of the way our immune system responds to influenza and influenza vaccines is resulting in new approaches to the development of vaccines that have more breadth in their ability to protect against a variety of influenza viruses.

Diagnostics Development

NIAID supports research aimed at improving influenza diagnostics to make them faster, more accurate, and usable wherever patients seek medical care. In particular, NIAID is funding the development of diagnostic platforms to examine the molecular makeup of influenza viruses to quickly distinguish between seasonal strains and those with pandemic potential. NIAID also supports development of influenza clinical assays to determine viral sensitivity to neuraminidase inhibitors – drugs that both lessen the severity and duration of illness in those infected, and potentially prevent infection in close contacts. To help ensure that patients receive prompt and effective care, NIAID will continue to develop rapid diagnostic tools that distinguish one influenza strain from another and also detect resistance to antiviral drugs.

Antiviral Therapies Development

Antiviral medications are important tools in treating and preventing complications of influenza infection. Three antiviral drugs (neuraminidase inhibitors) currently are recommended for the treatment of influenza in the United States. The emergence of antiviral-resistant influenza strains, however, requires the development of new and better treatment options. NIAID continues to pursue novel influenza therapeutics, including broad-spectrum antiviral drugs, and has advanced several candidates into clinical trials. NIAID supports the development of RNA polymerase inhibitors, peptide inhibitors, and next-generation neuraminidase inhibitors. NIAID also is developing monoclonal antibodies against hemagglutinin (HA), a protein on the surface of the influenza virus that enables it to attach to the cells lining the respiratory tract. Blocking the interaction between the virus and human cells with an antibody could prevent or lessen influenza disease. In addition, three NIAID clinical trials are underway to assess the effectiveness of novel influenza therapeutics in high-risk populations. These therapeutics include human plasma containing high levels of anti-influenza antibodies, concentrated immunoglobulin with high levels of anti-influenza antibodies, and a combination of three licensed influenza antiviral drugs.

Vaccine Development

Universal Influenza Vaccines

Annual influenza vaccination is the primary method to prevent seasonal influenza. Because influenza viruses evolve as they spread from person to person, the strains used in the influenza vaccine must be re-evaluated every year. When significant changes occur among circulating influenza strains after vaccine recommendations have already been made, the seasonal influenza vaccine may not be as effective in preventing influenza infection, as was the case with the H3N2

influenza A virus during the 2014-2015 influenza season. When genetic changes in the influenza virus cause substantial changes in the structure of its surface proteins, the strain that emerges can lead to a pandemic because a majority of the population lacks immunity to the new strain, as occurred with the 2009 H1N1 pandemic. We must constantly monitor evolutionary changes in circulating influenza viruses to be prepared for both seasonal and pandemic influenza. While recent analyses suggest that the strains in the current seasonal influenza vaccine match the circulating influenza strains, the mismatch experienced during the 2014-2015 influenza season underscores the importance of NIAID's sustained support for influenza research. In particular, the recent mismatch reminds us of the need for a more broadly cross-protective or "universal" influenza vaccine that could generate long-lasting protection against several influenza strains over multiple seasons.

NIAID research on universal vaccines is focused on several concepts, but the common principle behind each concept is to identify those parts of the influenza virus that are similar across multiple influenza strains and then maximize the immune system's ability to respond to them. Research on the HA protein has revealed that most influenza virus antibodies target the "head" of the HA protein structure, portions of which differ from strain to strain of influenza. In comparison, the "stem" of the HA protein is relatively stable among diverse influenza strains, suggesting that strategies to generate immune responses against the HA stem could elicit broader protection against multiple influenza strains. To explore this concept, NIAID is investing in universal influenza vaccine research and development focusing on the HA stem region, including early clinical trials of several vaccine candidates.

NIAID, in collaboration with BARDA, is continuing to support the development of HA stem-based universal influenza vaccines and other promising universal influenza candidates. NIAID intramural researchers also have developed a ferritin nanoparticle vaccine based on a stabilized HA stem from an H1N1 influenza virus. The vaccine, which lacks the HA head to more effectively elicit an immune response against the stem, protected against lethal influenza infection in animal models. Notably, the vaccine protected against a different HA subtype (H5) than the H1 subtype it was based upon, providing proof-of-concept that vaccines targeting the HA stem can offer broad protection against diverse influenza subtypes.

NIAID Vaccine Research Center (VRC) scientists also have conducted several clinical trials of another novel influenza vaccination strategy to assess whether it can induce enhanced and broadly reactive antibody responses. In this strategy, an initial vaccination with an influenza virus DNA vaccine known as a "prime" is followed by a "boost" with traditional seasonal influenza vaccine in an effort to improve the potency and durability of seasonal influenza vaccination. Three recent Phase I clinical trials investigating a regimen of an HA-based DNA influenza vaccine prime followed by a boost with either traditional seasonal influenza vaccine or a monovalent influenza vaccine found the vaccines were safe and produced an immune response. NIAID scientists also have discovered that mice inoculated with a virus-like particle vaccine were protected from infection with a wide range of influenza A strains, including strains not contained in the vaccine, suggesting another potential strategy to develop a universal influenza vaccine. NIAID is evaluating these vaccine strategies to better understand how they could contribute to universal influenza vaccine design.

Although we cannot predict when a universal influenza vaccine would be publicly available, NIAID-led efforts have generated encouraging progress toward this goal. It is important to note that as we develop universal influenza vaccines, promising candidates will need to be evaluated over several influenza seasons to determine the extent and durability of their protection.

New Vaccine Development Technologies and Pandemic Vaccine Approaches

NIAID is supporting efforts to develop and test a flexible vaccine manufacturing process for influenza vaccine development, including use of modern molecular biological techniques to help increase production efficiency and shorten manufacturing times. NIAID and industry partners are investigating recombinant DNA manufacturing that could be rapidly mobilized with the emergence of a pandemic virus. In addition, NIAID has supported investigation of improved strain selection and optimized high-yield vaccine strains as part of the Influenza Vaccine Manufacturing Improvement Initiative, a collaboration with ASPR/BARDA, CDC, FDA, and vaccine manufacturers. NIAID also supported the development of antigenic cartography, a computational method to understand evolutionary changes in influenza; this new method is now being applied to data from WHO Collaborating Centers to help provide information relevant to the composition of the annual seasonal influenza vaccine. An NIAID-supported computational method known as "antibody landscaping" has enabled scientists to visualize how the human immune system responds to a lifetime of influenza infections; this technique is now being used to aid in the design of "antigenically advanced" vaccines that may allow us to vaccinate against influenza strains that have not yet emerged in nature.

For decades, NIAID has conducted and supported research to prepare for the possible emergence of pandemic influenza. NIAID is currently supporting clinical trials of vaccines against H5N1,

variant strains of H3N2, and H7N9 to assess the immune responses these candidate vaccines induce in humans. Furthermore, NIAID is partnering with BARDA to investigate the safety and immunogenicity of an inactivated H5N8 vaccine with and without two stockpiled adjuvants designed to boost immune responses. H5N8 influenza is a novel strain of highly pathogenic avian influenza that has caused some of the outbreaks of disease in U.S. poultry populations and wild birds that have occurred since late 2014. These studies will inform potential "dose-sparing" strategies to maximize the supply of stockpiled vaccines in the event of a pandemic. In addition, NIAID intramural scientists are conducting clinical studies of prime-boost vaccine regimens for swine (H1) and avian (H7) influenza viruses, and collaborating with industry and BARDA to develop live, attenuated vaccines against potentially pandemic influenza viruses.

Other Clinical Research

NIH scientists are investigating human influenza infection under controlled conditions through clinical research with healthy volunteers challenged with influenza virus. These studies will help scientists more precisely define the timeframe between exposure to influenza virus and viral shedding, and the timing for the onset and duration of influenza symptoms as well as the development of an immune response. The scientists also are searching for factors correlated with protection against influenza. The findings of these studies are informing the design of clinical trials to evaluate candidate influenza countermeasures. For example, building upon NIAID research, an ongoing Phase II trial at the NIH Clinical Center is evaluating the efficacy of a novel monoclonal antibody targeting the stem of the influenza HA protein. In addition, NIAID, through its Vaccine and Treatment Evaluation Units (VTEUs), the Institute's longstanding clinical trials network for rapid testing of candidate vaccines and therapeutics, recently conducted a Phase II

clinical trial of a candidate H7N9 avian influenza vaccine. The study investigators found that two doses were able to generate immune responses in up to 84 percent of volunteers, but only if the vaccine was mixed with an immune-boosting adjuvant. The VTEU trial results provide additional clues to the development of effective H7N9 vaccines.

Conclusion

NIAID has a long history of research to develop better influenza diagnostics, therapeutics, and vaccines. Sustained support of NIAID's basic, translational, and clinical influenza research will contribute important information toward the advancement of an effective universal influenza vaccine that could provide lasting protection against multiple strains of influenza as well as prepare us for the next influenza pandemic. NIAID will continue to focus on advancing new tools to combat influenza in collaboration with government, academia, and industry partners.

Mr. MURPHY. Thank you. Dr. Midthun, you are recognized for 5 minutes, and please try and keep it to 5 minutes. We are running over. Thank you.

STATEMENT OF KAREN MIDTHUN

Dr. MIDTHUN. Mr. Chairman, Ranking Member DeGette, and members of the subcommittee, I am Dr. Karen Midthun, Director of the Center for Biologics Evaluation and Research, the center within FDA responsible for regulating vaccines. Thank you for this opportunity to be here today to discuss FDA's role in the highly collaborative effort in preventing influenza through vaccination in the United States.

Each year, influenza causes illness in a large proportion of the U.S. population and may result in serious complications including hospitalization and death. Influenza viruses continually undergo changes in their genetic makeup and resulting proteins that interact with the immune system. Therefore, the composition of influenza vaccines must be periodically updated to be effective against circulating viruses anticipated to predominate in the upcoming season. The strains of virus and the vaccine include two distinct subtypes of influenza A and one or two influenza B strains depending upon whether the vaccine is trivalent or quadrivalent.

To identify vaccine strains likely to cause illness during the upcoming season, the WHO convenes experts to study recently circulating influenza viruses from around the world and recent global disease patterns. Based on this assessment, the WHO makes recommendations on the composition of influenza vaccines usually in late February for the upcoming season in the Northern Hemisphere and in September for the upcoming season in the Southern Hemisphere. The recommendations must be made months in advance because of the time required for manufacturing, testing, lot release, and distribution of a very large number of vaccine doses.

Each year following the WHO recommendations, FDA convenes its Vaccines and Related Biological Products Advisory Committee typically in late February or early March. The committee considers the WHO recommendations and reviews information regarding viruses that caused illness in the previous year, how these viruses are changing and disease trends. Based on the data available at the time of the meeting, the committee makes a recommendation for the composition of influenza vaccines licensed by FDA for use in the U.S. during the upcoming season.

Once the strains are selected, candidate influenza viruses that are adapted for high growth are generated and accepted by the World Health Organization Collaborating Centers and are provided to manufacturers to generate the seed viruses for manufacturing vaccines. FDA then confirms the antigenic suitability of the manufacturers' seed viruses. The manufacturing demands are tremendous and the time lines are tight. No other vaccine is produced. FDA approved and distributed every year across the U.S. within a 6 month time frame. More than 170 million doses will be manufactured.

Given the yearly need for new vaccine, there is limited flexibility in the time lines for vaccine manufacturing and availability.

In parallel with vaccine manufacturing, FDA develops and calibrates reagents that are provided to the manufacturers and our regulatory counterparts throughout the world. These reagents are used both by FDA and the manufacturers to test the vaccines for potency and identity before FDA approves the new U.S. formulation for distribution. Manufacturers submit their vaccine testing results, along with samples from each lot, to FDA for lot release. As FDA releases lots, the manufacturers can make these lots commercially available throughout the U.S.

Every year, FDA begins working with manufacturers at the earliest stage of the influenza vaccine development process and we continue to assist throughout the production phase. We engage companies and technical and manufacturing issues and conduct facility inspections as warranted to ensure compliance with good manufacturing practice.

As part of the efforts to improve public health emergency preparedness for seasonal and pandemic influenza, HHS staff with expertise in influenza convene monthly at the Pandemic and Seasonal Influenza Risk Management Meeting. This group deliberates policy and programmatic issues regarding influenza medical countermeasures.

HHS has taken a series of steps to increase the probability that a late season change to trivalent or quadrivalent vaccine could be made or that a supplemental monovalent vaccine could be produced if warranted. Several actions by HHS for immediate implementation were proposed and tested and will be further refined based on a tabletop exercise that was conducted on November 10 with HHS agencies, vaccine manufacturers, and other global partners.

In spite of the difficulties inherent in preparing influenza vaccines, we have made progress in our preparedness efforts in collaboration with BARDA, CDC, NIH, and other stakeholders and we thank Congress for support of these efforts. New influenza vaccines have been licensed including cell-based vaccines, recombinant protein vaccines, and quadrivalent vaccines. To enhance pandemic preparedness, FDA licensed an adjuvant of H5N1 avian influenza vaccine and has worked with U.S. Government partners and manufacturers to facilitate the development of candidate vaccines directed at H7N9 avian influenza A.

Surveillance efforts are more extensive than ever before and offer the potential for early detection of emerging influenza viruses. The number of candidate vaccine virus strains available to manufacturers has increased greatly over the last few years, providing them with more options to increase vaccine yields. We continue efforts with our Government partners to develop high yield candidate vaccine strains, as well as more modern, faster methods to measure vaccine potency and sterility.

To further address the challenges presented by the constantly changing nature of influenza viruses, scientists affiliate with Government, academia, and vaccine manufacturers are working to develop a new generation of vaccines that might provide longer-lasting and broader protection including against drifted strains. Although these development efforts are still in early stages, some may have the potential increase and broaden protection against influenza. We will work with U.S. Government partners, manufactur-

ers, and other stakeholders to continue to facilitate the development of new vaccines and identify methods that have the potential to speed manufacturing process.

I thank you and look forward to any questions you have.

[The prepared statement of Dr. Midthun follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

KAREN MIDTHUN, M.D.

DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
COMMITTEE ON ENERGY AND COMMERCE
U.S. HOUSE OF REPRESENTATIVES

"U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?"

November 19, 2015

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman, Ranking Member DeGette, and Members of the Subcommittee, I am Dr. Karen Midthun, Director of the Center for Biologics Evaluation and Research (CBER), which is the Center in the Food and Drug Administration (FDA or the Agency) responsible for regulating vaccines. Thank you for the opportunity to be here today to discuss FDA's role in the highly collaborative, multi-partnered effort in preventing influenza through vaccination in the United States.

Influenza is a major public health concern that annually causes illness in a substantial proportion of the U.S. population and may result in serious complications, including hospitalization and death. Influenza viruses are highly unpredictable, and each year can present new challenges for vaccine manufacturers, public health agencies, the medical community, and patients. This year there is a record amount of influenza vaccine available, which continues to be antigenically well-matched to viruses that have been circulating to date. It is estimated that 171-179 million doses of vaccine will be available for the 2015-2016 influenza season. In 2015, there are seven U.S.-licensed manufacturers who make 14 licensed seasonal influenza vaccines, including some vaccines manufactured using novel technologies.

Influenza viruses continually undergo changes in their genetic makeup and the resulting proteins that interact with the immune system. These changes can occur from one season to the next; they can also occur within the course of an influenza season. Unlike other vaccines, the composition of influenza vaccines must be periodically updated so that they are effective against

what are anticipated to be the predominant circulating viruses in the upcoming influenza season. The strains of virus used in vaccine production include two distinct subtypes of influenza A (H1N1 and H3N2) and one (for trivalent vaccine) or two (for quadrivalent vaccine) different lineages of influenza B (B/Yamagata and B/Victoria, which are genetically divergent from each other).

Virus Strain Selection—A Worldwide Process to Ensure the Timely Availability of Influenza Vaccine

The process of ensuring the timely availability of influenza vaccine in the United States and elsewhere is a global, year-round process. Each year, the World Health Organization (WHO) convenes technical consultations in February and September to recommend the virus strains for inclusion in influenza vaccines for the Northern and Southern Hemispheres, respectively. FDA participates in both of these technical meetings. To identify virus strains likely to cause illness during the upcoming influenza season, influenza experts from WHO Collaborating Centers for Influenza (which include the Centers for Disease Control and Prevention (CDC)), the WHO Essential Regulatory Laboratories (which include FDA's CBER), and other influenza and public health experts study recently circulating influenza viruses from around the world and recent global disease patterns. In addition, blood samples from individuals receiving the most recent influenza vaccines are analyzed by the WHO Essential Regulatory Laboratories and WHO Collaborating Centers to determine how well antibodies induced by these vaccines react to recently isolated viruses. After careful evaluation of the antigenic and genetic characteristics of influenza viruses that are circulating and infecting humans across the globe and the ability of current vaccines to protect against these viruses, WHO makes recommendations on the composition of the influenza vaccines for use in the upcoming influenza season. These

recommendations are taken into account by national vaccine regulatory agencies, such as FDA, and vaccine manufacturers as they consider the vaccine composition for the upcoming season. WHO usually makes its vaccine strain recommendations in February for the upcoming influenza season in the Northern Hemisphere and in September for the upcoming influenza season in the Southern Hemisphere. The recommendations must be made months in advance of the next influenza season because of the time required for manufacturing, testing, lot release, and distribution of a very large number of vaccine doses consisting of antigens derived from three or four different influenza virus strains.

FDA's Role and the Manufacturing Process

WHO recommendations resulting from the technical consultations described above provide a guide to national public health authorities and vaccine manufacturers for the development and production of influenza vaccines for the upcoming influenza season. In the United States, FDA is responsible for regulating vaccines. In this role, FDA brings together public health and influenza disease experts to recommend which influenza virus strains should be included in FDA-licensed vaccines. FDA convenes its Vaccines and Related Biological Products Advisory Committee (VRBPAC) each year, typically in late February or early March and within a few weeks after the WHO consultation on influenza vaccine composition.

The VRBPAC considers the recommendations made by the WHO regarding the composition of influenza vaccines for the upcoming influenza season in the Northern Hemisphere. The committee also reviews information regarding viruses that have caused human illness in the previous year, how these viruses are changing, and disease trends. The information considered

in the review is provided in large part by CDC and WHO laboratories throughout the world. Based on the data available at the time of the meeting, the Advisory Committee makes a recommendation for the composition of influenza vaccines licensed by FDA for use in the United States during the upcoming season.

High growth candidate influenza viruses, which have been generated and accepted by WHO collaborating centers, are provided to the licensed vaccine manufacturers to generate the "seed viruses" for manufacturing their influenza vaccines. FDA confirms the antigenic suitability of the manufacturer's seed viruses. The manufacturing demands for influenza vaccines are substantial; there is no other vaccine that has to be produced, FDA-approved, and distributed every year across the United States within a six-month time frame. The manufacturing timelines are tight and the process of producing influenza vaccine involves many sequential steps and overlapping processes. Even with technologic advancements, each of these steps and processes still requires time to complete. Given the yearly need for a new vaccine, there is limited flexibility in the timelines for influenza vaccine production and availability.

Manufacturing of each antigen to be included in the vaccine occurs sequentially over several months, usually from December (produced at risk by the manufacturer before the strain recommendations are made) until late May. In parallel with vaccine manufacturing, FDA develops and calibrates reagents which are provided to the vaccine manufacturers and our regulatory counterparts throughout the world. Manufacturers and FDA use these reagents to test the vaccines for potency and identity before FDA approves the new formulation of the licensed seasonal influenza vaccines for U.S. distribution. The vaccines are formulated into standard

dosages, filled and finished by the manufacturers into final containers such as vials, syringes, and sprayers. Manufacturers submit their vaccine testing results, along with samples from each lot, to FDA for "lot release." As FDA releases lots, the manufacturers can make these lots commercially available throughout the United States. Typically, FDA approves the updated seasonal influenza vaccines with new labeling by the end of July. Every year, FDA begins working with manufacturers at the earliest stages of influenza vaccine development, and we continue to assist them throughout the production phase. During this period, we engage the companies on technical and manufacturing issues and conduct facility inspections to ensure compliance with good manufacturing practice, as warranted.

2015-2016 Influenza Season

FDA's VRBPAC met on March 4, 2015, to select the influenza viruses for the composition of the influenza vaccine for the 2015-2016 U.S. influenza season. During this meeting, the Advisory Committee reviewed and evaluated the surveillance data related to epidemiology and antigenic characteristics of recent influenza isolates, serological responses to 2014-2015 vaccines, and the availability of candidate strains and reagents. The Committee recommended that the trivalent influenza vaccines for the U.S. 2015-2016 influenza season be produced with the following: an A/California/7/2009 (H1N1)-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus, and a B/Phuket/3073/2013-like virus. The Committee also recommended that quadrivalent influenza vaccines be produced with the above three strains and the following additional B strain: a B/Brisbane/60/2008-like virus.

As noted earlier, the influenza vaccine continues to be antigenically well-matched to viruses that have been circulating to date, based on surveillance and testing conducted by CDC and other WHO Collaborating Centers. Manufacturers have projected that they will provide approximately 171 to 179 million doses of vaccine for the U.S. market, a record amount.

Department of Health and Human Services (HHS) Preparedness Efforts in the Event of a Future Seasonal Influenza Vaccine Mismatch

As part of the efforts to improve public health emergency preparedness for seasonal and pandemic influenza, HHS staff with expertise in influenza convene monthly at the Pandemic and Seasonal Influenza Risk Management Meeting (also known as the Flu Risk Management Meeting (FRMM). Participating agencies include HHS (ASPR, the Biomedical Advanced Research and Development Authority (BARDA), the Assistant Secretary for Health's National Vaccine Program Office, FDA, the National Institutes of Health (NIH), and CDC), the Department of Homeland Security, and the Department of Veterans Affairs. This group deliberates policy and programmatic issues regarding influenza medical countermeasures. Discussions include an end-to-end approach from basic research to the advanced development of new medical countermeasures to distribution and utilization strategies.

In response to the mismatch that occurred between the 2014-15 seasonal influenza vaccine and circulating H3N2 viruses that had undergone antigenic drift, the interagency working group developed an action plan that may mitigate future occurrences of such an event. HHS has taken a series of steps to increase the probability that a late season change to tri-or quadrivalent vaccine

could be made or that a supplemental monovalent vaccine could be produced, if warranted. In June 2015, ASPR hosted a meeting with vaccine manufacturers, international public health partners, and HHS representatives to solicit opinions on HHS recommendations and plans to address potential seasonal influenza vaccine mismatches due to viral antigenic drift. Several proposed actions by HHS for immediate implementation included the following:

1) Work with the WHO to expand influenza strain surveillance capacity that ensures greater and earlier detection of emerging influenza viruses globally that may have drifted antigenically, thereby, informing decisions on generating more vaccine viruses sooner.
2) If antigenic drift is identified after the WHO and FDA's VRBPAC make their seasonal vaccine strain recommendations in February or early March, CDC and FDA will apprise HHS senior leadership, and together with WHO, will notify the manufacturers. In addition, FDA will notify the Chair of VRBPAC. This formalizes the previous communication practices.
3) If there is evidence of antigenic drift, CDC will provide candidate vaccine viruses (for egg and cell-based vaccines) that are antigenically similar to the drifted strain and provide the new candidate vaccine viruses to the manufacturers for production testing.
4) In the event of suspected antigenic drift, FDA will develop matched vaccine potency reagents for the new candidate vaccine viruses and make them available to manufacturers.

These and other steps have been tested and will be further refined based on a tabletop exercise that was conducted on November 10, 2015, with HHS agencies and vaccine manufacturers as

individual participants, to solicit their individual opinions. The exercise outcome is expected to inform an HHS action plan for rapid development and manufacturing of a revised trivalent or quadrivalent seasonal influenza vaccine or a supplemental monovalent vaccine. The FRMM leadership also recommended to HHS leadership additional action items to implement over the immediate, interim, and long-term horizons (18 months – five years) to address vaccine mismatch issues in the areas of virus surveillance and characterization, technologies, vaccine design, and vaccine distribution. Together with the influenza vaccine manufacturers, federal agencies, WHO and its collaborating laboratories, and regulatory authorities and public health leadership in other countries, a coordinated action plan may be adopted to address antigenic drift and vaccine mismatch problems.

Progress in Influenza Vaccine Manufacturing

In spite of the difficulties inherent in preparing influenza vaccines, we continue to make progress in our preparedness efforts in collaboration with BARDA, CDC, NIH, and other stakeholders. For example, FDA has licensed numerous new influenza vaccines over the past decade, including cell-based influenza vaccines, recombinant protein vaccines, and quadrivalent influenza vaccines. Cell-based and recombinant protein influenza vaccines provide an alternative to the traditional egg-based process of manufacturing, and provide the potential for a faster start-up of the vaccine manufacturing process. FDA licensed the first cell-based influenza vaccine, Flucelvax, manufactured by Novartis, in November 2012, and the first recombinant influenza vaccine, FluBlok, manufactured by Protein Sciences, in January 2013. In addition, FDA has licensed quadrivalent influenza vaccines from four different manufacturers since 2011. Prior to the licensure of quadrivalent vaccines, all FDA-licensed vaccines were intended to

protect against two influenza A strains and one influenza B strain. The quadrivalent vaccines are intended to protect against two influenza A strains and two influenza B strains, representing the two B lineages that often are co-circulating in any given season. To enhance pandemic preparedness, in 2013, FDA licensed an adjuvanted H5N1 vaccine, manufactured by GlaxoSmithKline Biologicals, and has worked with U.S. Government partners and manufacturers to facilitate the development of candidate vaccines directed at H7N9 avian influenza A.

Surveillance efforts are more extensive than ever before and offer the potential for early detection of emerging influenza viruses. The number of candidate vaccine virus strains available to manufacturers has increased greatly over the last few years, providing them with more options to increase vaccine yields. FDA, in conjunction with BARDA, CDC, and NIH, continues efforts to develop high-yield candidate vaccine strains, as well as more modern, faster methods to measure vaccine potency and sterility. To further address the challenges presented by the constantly changing nature of influenza viruses, scientists in government laboratories, academic institutions, and vaccine manufacturers are working to develop new-generation vaccines that might be longer-lasting and provide broader protection against drifted strains. Although these vaccine development efforts are still in early stages, some may have the potential to increase and broaden protection against influenza. FDA will continue to work with U.S. Government partners, manufacturers, and other stakeholders to facilitate development of new vaccines and identify methods that have the potential to speed the manufacturing process for existing vaccines. Our goal is to better protect the American public, including those at higher risk of complications from influenza.

Mr. MURPHY. Thank you. Since we are going to vote soon, we will get to as many as we can and then take a break and come back.

Let me start off and recognize myself for 5 minutes. Dr. Schuchat, have the influenza strains grown increasingly complex and are they being distributed more broadly across the globe now?

Dr. SCHUCHAT. CDC has expanded our surveillance so that we do have testing of viruses from more and more places, but we actually need to do even more. The H3N2 virus that was predominant last year really showed us that these strains have evolved away from the tools that we have been using. We have had to modernize our tools and move to a sequence first approach which helps us overcome the old HI test that wasn't really helping us understand the distribution of strains. So there have been important changes in the evolution of H3N2 that have made it difficult with the old tools to track what is going on.

Mr. MURPHY. And there has been a large increase in human infections with the influenza A virus over the past 20 years. And is it true that there are many new types of highly infectious influenza strains the world is racing to keep up with, a wider range of types?

Dr. SCHUCHAT. We have increased the sophistication of testing so we are picking up unusual types, the types that jump from animals to people. We have seen more of those. It is difficult to say whether this is happening more or we are finding it more. We really have increased the global capacity of countries all around the world to recognize influenza, test for it, and provide specimens that can be further characterized.

Mr. MURPHY. But as you are talking about those global aspects, is part of this also that there is the issue of increased international travel and trade that is also spreading faster and influencing some of this?

Dr. SCHUCHAT. There are so many factors that have made infectious threats greater and greater today. The closeness with which animals and people interact these days, some of the manufacturing or agricultural practices around the world, of course, travel and trade means that people are in contact with each other in different ways. So not just for influenza, but for many threats, we really see infections anywhere. Could be here at home soon.

Mr. MURPHY. So what you are talking about then is you are picking up more. There is increased threat and unpredictability, but has the flu modeling really changed to more accurately reflect the best information of flu viruses, specifically is it being changed to more accurately prepare for an influenza vaccine?

Dr. SCHUCHAT. The application of modeling approaches to the genetic data has advanced substantially. We have an enormous amount of genetic sequence data now that is being used in more sophisticated ways. So we think this is a very important tool for the future to actually use modeling really to predict what would be better reassortants that could make better vaccines.

Mr. MURPHY. And in another area, Doctor, are serum banks useful for testing candidate viruses for the flu vaccine? And if so, could more use of serum banks help provide better sampling for testing candidate viruses?

Dr. SCHUCHAT. I am probably not the best person to answer that question.

Mr. MURPHY. Who would be?

Dr. SCHUCHAT. But I could begin.

Mr. MURPHY. OK.

Dr. SCHUCHAT. Basically, the ways we are testing candidate vaccine viruses or that we are testing circulating viruses include old tools and new tools. We have been using this HI hemagglutinin inhibition test which was developed in the '40s and is really not working anymore for many of these difficult strains. We are switching to neutralization assays and to synthetic receptor models that we would like to invest in.

Serum banks isn't sort of the cornerstone of how we would be going about this, but there may be others who want to try and answer.

Mr. MURPHY. Does anybody else have any thoughts on that? If not, I will go to my next question. OK.

So are there any studies currently underway examining the immunological profile throughout our country to determine if there is any regional differences on what influence of viruses are predominant and what traces of immunity are in local populations?

Dr. SCHUCHAT. You know, that is a very interesting question.

Mr. MURPHY. That is why I asked it.

Dr. SCHUCHAT. OK. You know, we have expanded our Vaccine Effectiveness Network in the U.S. to have more communities included in larger numbers. One thing that we found last year with the difficult strain that we had in the drift was the vaccine effectiveness was poor generally, but in one area which happens to have been Pennsylvania, the vaccine worked quite well and we think that the strains that were circulating in Pennsylvania were of a different clade or subtype. They were the old strain, not the drifted one. So in fact, the vaccine worked better than most places in Pennsylvania.

We think it is really important for us to have lots of viruses and to test them with the best tools so that we really can understand what is circulating and that we need very good vaccine effectiveness platforms, both in the United States and in the Southern Hemisphere to really understand how the vaccines are performing in actual use, not just predicted to perform through the lab assays before we start using them.

Mr. MURPHY. Thank you. My time has expired. I now recognize Ms. DeGette for 5 minutes.

Ms. DEGETTE. Thank you, Mr. Chairman. I am always encouraged to hear researchers and experts come in and talk about the new development methods that we are beginning to achieve for flu vaccine, but Dr. Midthun, we are still primarily using egg-based technology to produce the flu vaccine right now in this country, correct?

Dr. MIDTHUN. It is correct that most of the influenza vaccine is produced with egg-based technology.

Ms. DEGETTE. And one of the problems with egg-based technology is that obviously it takes time if the virus should mutate or need to be changed. Is that correct?

Dr. MIDTHUN. It does take time, but it also takes time if you make the product using cell-based or recombinant technologies. There may be some time savings, but nonetheless you need to be

able to have the virus that will grow well in the cell base as well as well as the——

Ms. DEGETTE. But the other problem, as we have seen in past hearings, is that if you have some kind of pandemic, then the additional problem to the time it takes to grow the virus in the eggs is the egg availability. We saw that with the avian flu and other things. Is that correct?

Ms. DEGETTE. You know, I might ask Dr. Robinson to add here, but actually a lot has been invested in both——

Ms. DEGETTE. But all I am asking is it takes a lot longer if you have to rapidly grow vaccine in eggs to get the eggs, yes or no?

Dr. MIDTHUN. It depends. In general, it is possible to get a virus that will grow more quickly in a cell-based system than an egg-based system.

Ms. DEGETTE. Look. I have 5 minutes. Yes or no. If you have to increase egg production it takes a long time. Is that right? OK, never mind. You are not going to answer my question.

Let me ask you, Dr. Robinson, because you testified that we have developed a lot of these new technologies, but they are not being used on a routine basis for the seasonal vaccine. Isn't that correct?

Dr. ROBINSON. So both recombinant and cell-based vaccines are licensed for seasonal purposes.

Ms. DEGETTE. That is correct, but they are not being used widely. Isn't that correct?

Dr. ROBINSON. That is correct.

Ms. DEGETTE. OK, why is that?

Dr. ROBINSON. They are competing when the incumbent vaccine industry where you have egg based and they are new to the enterprise and they are fighting it out in the markets.

Ms. DEGETTE. Part of the problem is it is a market-based technology?

Dr. ROBINSON. Correct.

Ms. DEGETTE. And so it costs more money, right?

Dr. ROBINSON. So far, that is correct.

Ms. DEGETTE. How do you see the markets moving particularly with development of pandemic types of vaccines? Would we be able to be nimble enough to use those new technologies if we had some kind of pandemic flu and how long would it take us to ramp up?

Dr. ROBINSON. So to answer your question, yes, they are part of what we do for pandemics. They have been part of what we have developed and they are part of our capacity to make the U.S. independent of other countries providing those vaccines.

Ms. DEGETTE. How long would it take? Because right now, we don't have a stockpile of pandemic flu vaccine.

Dr. ROBINSON. We have stockpiles for H5N1 and H7N9. The new pandemic——

Ms. DEGETTE. Some of those are 10 years old, right?

Dr. ROBINSON. And we are actually testing those exactly right now in fact to see whether or not they are still good.

Ms. DEGETTE. Can you supplement your testimony to let us know if they are still good?

Dr. ROBINSON. I would be happy to.

Ms. DEGETTE. Once you finish that. That would be good. But so let us say we had a new strain of avian flu or some other kind of

pandemic flu. How long would it take us to develop those vaccines then?

Dr. ROBINSON. Having been around for the H1N1, we took about 23 to 25 weeks for us to start to actually have vaccine available in October of 2009. H7N9, 2013, we actually broke that record by several weeks, in fact, and we now have more tools that we can actually do it a little bit faster if we start for a new pandemic virus.

Ms. DEGETTE. So you think you could go down to like 20 weeks?

Dr. ROBINSON. Our goal, our aspirational goal is to actually have the vaccine in 4 months.

Ms. DEGETTE. OK, so the problem is, of course, which we all understand is if you see a pandemic flu, 4 months is going to be a long time to try and develop a new vaccine. Are there ways that you think with our support we could get that even shorter?

Dr. ROBINSON. Certainly if we can keep all of these manufacturers going for seasonal influenza vaccine markets, then we have a greater chance to have those available and make larger predominance of those vaccines available, both seasonal and pandemic.

Ms. DEGETTE. I am out of time and I know we are trying to get a lot of questions in, but I am going to have a lot more answers that I would love it if you guys could respond in writing. Thank you.

Mr. MURPHY. Thank you. We will have time for Mr. Collins for 5 minutes.

Mr. COLLINS. Thank you, Mr. Chairman. Maybe to follow up a little bit on Ms. DeGette's questions, Dr. Robinson, on the pandemic flu, the H5N1 that has been stockpiled for 10 years, what is your—since it has never jumped to humans, H5N1, right?

Dr. ROBINSON. There has been a number of individuals that have been infected with H5N1. It is highly lethal.

Mr. COLLINS. Right, but didn't jump.

Dr. ROBINSON. It is not easily transmitted.

Mr. COLLINS. Correct.

Dr. ROBINSON. From man to man.

Mr. COLLINS. Correct. So on what basis did you characterize or decide how to produce the H5N1 vaccine since it has never really jumped from animals to humans?

Dr. ROBINSON. So we have been working over about 10 years putting together the H5N1 vaccine development plans with our colleagues at FDA, NIH, and also at CDC and with industry partners. And we actually were able to successfully make the first one that was licensed in 2007, more recently with adjuvants were licensed 2013. And we were able to actually show that we can actually produce at very high levels, and we can do it quickly. We actually had experience in 2013 for another avian influenza virus, H7N9, in which we were able to use egg, cell, and even recombinant technologies to make those vaccines sooner using all the new methods that we have.

Mr. COLLINS. So let us say that something happens and it does become a pandemic. Is your organization looking at any post-symptomatic treatments for a person—it is so deadly, especially in this case, healthy individuals, for any kind of post-symptomatic treatments?

Dr. ROBINSON. So we have invested very heavily in new antiviral drug candidates and some of those have actually been approved by the FDA. Preamivir was in 2014. We are looking at non-neuraminidase inhibitor type of molecules and also immunotherapeutics, antibodies that be used to treat——

Mr. COLLINS. Monoclonal or polyclonal?

Dr. ROBINSON. In our case, monoclonals. There a number of good candidates out there and we have started supporting those.

Mr. COLLINS. Why not a polyclonal?

Dr. ROBINSON. So if there are good candidates, we certainly wouldn't be looking at those presently. The monoclonals look like they have several advantages.

Mr. COLLINS. I am not sure what the advantages are since they target a specific—on anything that mutates as rapidly as this virus——

Dr. ROBINSON. So they actually are targeted to regions of the virus that do not mutate. They are highly conserved.

Mr. COLLINS. So is your opinion the stockpile we have adequate if something were to happen?

Dr. ROBINSON. So for the antiviral drug stockpile that we have, the Strategic National Stockpile is responsible for. It is designed and is equipped to handle what we would have for severe influence of pandemic.

Mr. COLLINS. So a question on the adjuvant. You have done that only to make it a more potent, if you will, vaccine that would——

Dr. ROBINSON. So for originally why we actually used adjuvants is because it was going to take so much vaccine and so many eggs at the time when we started the work that we couldn't have enough.

Mr. COLLINS. Makes it more potent.

Dr. ROBINSON. Makes it more potent. But it actually also allows now, we understand, for the vaccine to actually protect against different strains of influenza.

Mr. COLLINS. I know our time is running out, but make a question for Dr. Schuchat, the elderly sometimes are more at risk just because of their health. Is that a population where we might decide to have two versions of even the seasonal vaccine, one adjuvanted, one not, and have those over whatever 65 or in poor health, have the adjuvanted vaccine?

Dr. SCHUCHAT. You know, right now there are more than one formulation for the elderly, so a high dose vax formulation has been licensed for the elderly and adjuvanted formulations are under review. So I think we really do focus on the elderly who suffer the most from influenza in most seasons with hospitalizations and deaths and in a pandemic typically, not the 2009 one, but typically would also suffer extensively. And we do think better vaccines are important for that population. There has been a lot of progress and there is more progress we look forward to in the future.

Mr. COLLINS. But currently, there is not an adjuvanted version of the seasonal?

Dr. SCHUCHAT. That is right, not yet. But there is one that is under review.

Mr. COLLINS. Yes.

Dr. MIDTHUN. Yes, we have a license application for an adjuvanted vaccine for individuals for seasonal vaccine, 65 years of age and older which was discussed in advisory committee 2 months ago and is currently under review. It shows, it compared the immune response to the adjuvanted versus the unadjuvanted and it did not actually show that the adjuvanted vaccine indicated a superior immune response, but nonetheless, we are considering this for licensure.

Mr. COLLINS. Thank you very much. My time has expired. I yield back.

Mr. MURPHY. Thank you. We have about 3 ½ minutes left in the vote. So we are going to break. We will back in about 40, 45 minutes, my guess. We will get right back to questions. We should get in all the questions in from all the Members before the second series of votes after that. So we will be back. Thank you. We are in recess.

[Recess.]

Mr. MURPHY. All right, we will reopen the hearing here, and now I will recognize the gentleman from Texas, Mr. Green, for 5 minutes.

Mr. GREEN. Thank you, Mr. Chairman. And I thank our witnesses for understanding our vote schedule on the floor and hope you had some rest between the questions earlier.

I represent a very urban district in Houston. It is actually medically underserved and so 20 years ago we started doing vaccinations for children in our elementary schools in August just before school started so we would raise our vaccination rate. And we have been doing that since then and it has been really successful. We partner with our local school districts, our county health department, Texas Children's Hospital, and so in a sense we have raised in our ZIP Codes, the percentage of children who are immunized. And I always talk about immunizations are the cheapest medical dollar we can ever spend because it is most effective.

Last weekend, we actually did a flu vaccine effort. Texas Children's Hospital did children's vaccines. Walgreens, our pharmacy, one of our chain pharmacies in our community, did adults and the seniors. We didn't get a good turnout because this was our first as compared to having 20 years of experience, people expect us in August to do the children's vaccines. But my concern was last year because of the effectiveness of the vaccine and we want more people to get the vaccine, but when you hear that it is 20 percent or so, give or take, efficiency, what can we do to help make sure that you have the tools to make that efficiency much better?

I know flu mutates. It is really a challenge. But we would hope we could do better than 20 percent. And I know that has been other questions and I would be glad to see what Congress can do to help the agencies be able to do a better job.

Doctor, if you want to start?

Dr. SCHUCHAT. Sure, I can start and I can pass it along. The people represented here, our institutions have been working really closely together to improve influenza vaccine both a seasonal flu vaccine pandemic and then future vaccines that might be even better. But from the CDC perspective, the more viruses from more places that we have characterized really well gives us information

that can lead to better candidate vaccine viruses that we can then turn over to FDA to make sure they are OK and to industry to produce. So sustaining that investment in strong surveillance around the world including newer approaches here at home with more samples coming in of the minority strains that we have and then sequence first so we get the information right that is actionable.

I did just want to say that that issue of will people even want to get vaccinated after the year that we had last year? We have been investing in communication research to really understand what is going on in people's minds, what are their attitudes so that we can sustain better and better immunization coverage going forward.

Mr. GREEN. OK, anybody else have——

Dr. ROBINSON. Yes, sir. We have had the mantra for a number of years of more and better vaccines sooner. We built capacity in the United States to have more. We are working on getting it made sooner. We are making it with new technologies and not just for cell- and recombinant but also even for egg-based to make those actually be made faster. That better part, actually more effective and efficacious vaccines is the one that NIH, Dr. Heilman and we are working on to actually address the problem of it being not 23 percent, but 75, 80 percent every year, year in and year out. That is our goal. We may never be able to attain it, but it is what we want to do and that is why the universal flu vaccine initiative that we work on and to be able to have funding to go forward with that, not just for one year, but multiple years, because that may take a long time to get there. But it will be the ultimate answer to this.

Dr. HEILMAN. I just want to thank you for your support of NIH and your recognition that research is really a foundation point for which to move forward on. And I think as Robin and Anne and Karen can attest to, you know, the ability for us all to get together to work on a common goal, we each have a contribution to this. So even though the things that we do are kind of a little bit more downstream, upstream, you know, it really does impact the opportunities for not just next season, but for seasons afterwards. We constantly want to evolve and improve whatever we are doing, so appreciation for the recognition that research has.

Mr. GREEN. I am almost out of time. Previously, in our committee both the Oversight and Investigations and our Health Subcommittee over the years, we were actually concerned about enough flu vaccines. I know a few years ago, there was a shortage early on. But again, it is hard. If we are going to continue vaccinate folks and say oh, I don't want one because it is not effective and I will get a sore arm anyway or something like that, we don't want to give people a reason because again for the elderly and for the disabled, the flu vaccine is so important because their immune systems are already challenged and we need to make sure it is as effective as we can.

Mr. Chairman, I thank you. And thank you for calling the hearing today.

Mr. MURPHY. Thank you. Now I will recognize Mr. Mullin of Oklahoma for 5 minutes.

Mr. MULLIN. Thank you, Mr. Chairman. Thank you for holding this. I have to admit I am one of those people that I am not sure if I have ever received a flu vaccine and however, there are a lot of people that are very consistent on getting one and I understand the importance of it. But I am concerned with the stockpiles that we have had.

Dr. Robinson, you have said in your opening testimony and the effort to stockpile the vaccines against a flu outbreak, but at the same time we also know that the flu changes constantly. And so for stockpiling it, how are we testing it? How are we knowing that what we are going to send out is actually going to be effective because we have already had one case, actually several cases that the vaccine that we sent out wasn't actually the one that we needed to target.

Is there something we can help you with? Is there a way that you are testing? Can you help me understand that a little bit?

Dr. ROBINSON. Thank you for the question. It is very appropriate because I want to explain that the vaccine that we stockpile is what we call pre-pandemic vaccines for viruses that potentially could cause a pandemic, like the avian influenza H5N1, the H7N9 viruses. For example, the H5N1 viruses appeared in 1998. We thought we got rid of them and they reappeared in 2003 and we still see cases and they spread from Southeast Asia across Asia into the Middle East and Europe.

We are always watching those viruses and we actually do a periodic risk assessment with our colleagues across the board here with CDC, FDA, NIH, and others in the Department and with experts across the world in which we look at that risk assessment to say is this virus still something to worry about? And so the stockpiles that we have, we actually made—every day that we have those stockpiles, they break a record. Usually we think that the flu vaccines you can only keep them around for about 12 months, maybe 18 months. Some of these are 8 and 9 years old. The potency of those vaccines is still very high.

Mr. MULLIN. How often do you test? Do you do a random test?

Dr. ROBINSON. No, we actually test every 3 months.

Mr. MULLIN. All?

Dr. ROBINSON. All the lots that we have and——

Mr. MULLIN. Every 3 months?

Dr. ROBINSON. Every 3 months. And now we are actually testing those in the clinic to actually answer the question to say a vaccine that has been around for 8 years versus one that is newly made, when we put those into people do they get the same immune response and just as important, do they well tolerate the vaccine.

Mr. MULLIN. So while we are looking at stockpiling for potential outbreaks, does that hurt us actually being able to manufacture enough of the current flu outbreak? Because we seem like we have shortages constantly.

Dr. ROBINSON. The time in which the manufacturers make these vaccines is when they are not making seasonal influenza vaccines. So it does not impact the ability for them to make their capacity for seasonal flu.

Mr. MULLIN. Dr. Schuchat, did I say that right? OK, and I apologize. We have been hearing from doctors back in Oklahoma that

they are having a hard time getting the vaccine, especially for children right now. And so we contacted the Oklahoma Health Department and they said there was a shortage, that they were having a hard time getting a hold of it. Are you familiar with this?

Dr. SCHUCHAT. You know, the flu vaccine distribution so far this year is quite good with 133 million influenza vaccine doses shipped around the country so far. But we do know that a couple of the companies have had some limited or delayed production of one or two of the pediatric formulations. It is still a lot of vaccine that is out there, but there may be some particular practices that don't have all the pediatric vaccine they want.

We also learned that there are some States that the way that they handle the vaccine for children vaccine that CDC buys and it is shipped to central distributors and managed by the States, that there are probably more efficient ways for them to allocate the vaccines to the pediatricians and their communities. So CDC and the Association of Immunization Managers are working with the State health departments to really try to make sure we are streamlining those distributions so that the docs are getting the product when they need them.

Mr. MULLIN. How often do you look at the product to say do we need to change it or not? And the reason why I say this is because my Larra, my 7-year-old daughter who was 6 at the time, last year she got two different strains of the flu.

Dr. SCHUCHAT. I am so sorry.

Mr. MULLIN. She got the shot. The first one she got and she still got it. The second one they said there wasn't a vaccine for it yet.

Dr. SCHUCHAT. OK, well one thing I can say is that we do vaccine effectiveness studies every year to see how well the vaccine is performing. You know the vaccines are often changed each year and people get vaccinated every year. And we have a network that is studying how well the vaccines actually protect people. We have expanded that network and we have increased how intensively they are working so we can get information sooner.

Last year, we were able to present interim results in January, the earliest ever, to know how the products were working.

Mr. MULLIN. Dr. Schuchat, thank you so much. And Dr. Robinson, appreciate your insight on that. I yield back.

Mr. MURPHY. Can I ask a follow-up question to what Mr. Mullin has asked? In terms of stockpiles, Dr. Robinson, what are the size of these stockpiles? Are they thousands, tens of thousands, millions?

Dr. ROBINSON. For H5N1s, we have tens of millions of doses and for H7N9, we have millions of doses.

Mr. MURPHY. It is just the two areas you have?

Dr. ROBINSON. Those are the two viruses. For H5N1, we have four different strains of H5N1 viruses represented in that stockpile and for H7N9 we have one strain.

Mr. MURPHY. And you were saying they are effective for 8 years so far?

Dr. ROBINSON. So far for the H5N1 vaccines, the potency is still very high for those stockpiles.

Mr. MURPHY. And you are holding on to those that if it erupts again, you are ready to go?

Dr. ROBINSON. So far, we don't have to throw them away. We can still use them and we can use with adjuvants to provide greater cross protection against even new H5N1 virus.

Mr. MURPHY. OK. Thank you. Mrs. Brooks, you are recognized for 5 minutes.

Mrs. BROOKS. Thank you, Mr. Chairman. And thank you for holding and highlighting this important issue. The hearing though is a reminder that public health threats like influenza are also threats and can be threats to our national security. The same issues we saw with last year's seasonal flu drifting and mismatched strains can happen with other influenza strains that can cause even deadlier pandemics. And obviously, the pandemic we experienced in 2009 with the H1N1 killed, as I have been told, 18,000 Americans and most people don't realize that. And if we think about that, we weren't prepared for that threat then and thousands of Americans lost their lives.

I am very proud to be working on some bipartisan legislation with my colleague, Congresswoman Eshoo, who has been a leader in this space, and other colleagues on this committee to improve our biodefense enterprise.

H.R. 3299, the Strengthening Public Health Emergency Response Act, would improve the medical countermeasure development process, would provide new incentives for the development of these lifesaving countermeasures and would strengthen our public health response capabilities.

And so, Dr. Robinson, in part because of this legislation, my questions are going to be directed primarily to you because obviously, it is the job of Congress to ensure that BARDA is doing, and I thank you, all of you for your work, but BARDA is doing everything it can to develop those medical countermeasures as quickly and as effectively as possible for pandemic outbreaks, and in the spirit of the focus today for pandemic influenza.

But I am going to ask you and maybe because I am a lawyer, I have some very specific questions I would like your answers to and I understand we have a former colleague on the committee, Congressman Dingell. A series of simple yes or no questions. I would like to ask you because they are relevant to the types of issues that we have identified in H.R. 3299. And if you wouldn't mind just giving me a yes or no and we can get into further discussion a bit later.

Do you believe that additional incentives are needed to get the private sector more involved in this risky, time-consuming, and costly endeavor of developing medical countermeasures?

Dr. ROBINSON. Yes.

Mrs. BROOKS. Thank you. Do you believe that the creation of the priority review voucher limited to the 12 material threats identified by the Department of Homeland Security already, would be a useful incentive to get the private sector interested in medical countermeasure development?

Dr. ROBINSON. Yes.

Mrs. BROOKS. Did Congress give BARDA a unique national security mission, something no other agency in HHS has currently?

Dr. ROBINSON. Yes.

Mrs. BROOKS. When Congress gave BARDA this unique mission, was BARDA also provided with unique contracting authority?

Dr. ROBINSON. Originally, yes.

Mrs. BROOKS. And do you believe it would be helpful to further expedite the medical countermeasures contracting process, to expedite that contracting process?

Dr. ROBINSON. We always look for ways to expedite.

Mrs. BROOKS. Thank you. And would it be helpful for you to have direct control over BARDA's advanced development and procurement contracts for medical countermeasures? Would that be helpful, yes or no?

Dr. ROBINSON. It would be helpful, anything that we can do to expedite, yes.

Mrs. BROOKS. OK. Thank you. And I understand that it has changed over time from its origin from when BARDA was created, but that is the basis and part of what Congresswoman Eshoo and my work is designed to do. And I would really like to ask all of you and Governor Ridge and Senator Lieberman have just released this incredible report, multiple recommendations. Can you talk to us, starting with you Dr. Robinson, whatever time I have left, in what more we can be doing as a Government to build up a robust, domestic production capability?

Dr. ROBINSON. Thank you for that question. I will answer briefly, but I can talk for hours on this.

Mrs. BROOKS. And we will at another time then.

Dr. ROBINSON. At this point, we need to continue the mission that we set out to do and that is to go forward with the early development that NIH does and advanced development that BARDA does to actually have those products available, not just for man-made threats and pandemic influenza, but emerging infectious diseases which Ebola showed it could be either one.

Secondly, where we can't stockpile, we need to do so. But in other instances, we need to have emergency response capabilities when we can't stockpile to actually have those available and have those capabilities of those technologies and many of those platform technologies going forward. We have made great strides with FDA being able to move us forward quickly and be able to have absolutely the regulatory capability to do that. I think we can do more though and they need to be funded to provide that capability going forward.

Mrs. BROOKS. Thank you. And thank you all very much for your work. I yield back.

Mr. MURPHY. The gentlelady yields back. I now recognize the gentleman from Virginia, Mr. Griffith, for 5 minutes.

Mr. GRIFFITH. Thank you very much, Mr. Chairman. In 2014, the Centers for Disease Control and Prevention Advisory Committee for Immunization Practices, ACIP, updated its adult vaccine schedule to recommend that older adults get a pneumococcal vaccine in conjunction with routine influenza immunization with a routine influenza immunization and a follow-up pneumococcal vaccine within 6 months.

When the recommendations were published, primary care physicians expressed some concern about the logistics of these recommendations and about Medicare reimbursement. Since that

time, the Centers for Medicare and Medicaid Services announced it would cover the second pneumococcal vaccine.

Dr. Schuchat, can you update us on these new recommendations and what CDC has done to work with primary care physicians on addressing their concerns and confusion?

Dr. SCHUCHAT. Thank you so much. The pneumococcal conjugate vaccine that targets 13 types was recommended initially by ACIP for everybody 65 and over in addition to the earlier polysaccharide vaccine, the 23-valent type, that we also have recommended for everybody 65 and over.

The summer of 2014—sorry, the summer of 2015, we updated those recommendations to simplify them because we had heard about the confusion that primary care physicians had and we changed them to make them simpler so that you get one pneumococcal conjugate vaccine when you turn 65 or later and the second one a year or more later.

CMS does cover two doses of pneumococcal vaccines and it doesn't matter which one comes first, but we regularly recommend getting a conjugate first. It is very important for seniors who are often hospitalized and can die and it is particularly important in influenza season because pneumococcal pneumonia frequently follows flu. So we recommend everybody 65 and over get an annual flu shot, and get an pneumococcal vaccine, the conjugate one, followed a year or more later by the 21-valent polysaccharide.

Mr. GRIFFITH. Also when ACIP makes its recommendations, does it consider how to ensure uptake is as efficient and streamlined as possible?

Dr. SCHUCHAT. It is a very important part of the recommendations. We have practitioners and public health experts who are members of the ACIP and we work closely with partners to implement the ACIP recommendations and make it easier for people to protect themselves and their families. So we work very closely with the American College of Physicians, the American Academy of Family Physicians and so forth to really make sure that it is easy to get a vaccine and to protect yourself and your family.

Mr. GRIFFITH. OK. According to the CDC's estimates, four in ten seniors are not vaccinated for pneumonia, meanwhile flu vaccination rates have not significantly increased for seniors in the last 15 years. How is CDC working with the internal medicine physicians and family physicians to improve vaccination rates among seniors and ensure seniors get the recommended flu and pneumococcal vaccines when appropriate?

Dr. SCHUCHAT. You know, one of the challenges with adults is that they still think vaccines are for kids and so both providers for adults, as well as adults themselves, often don't recognize that vaccines can be lifesaving for all of us.

In addition to working with the clinical community, CDC works closely with the private sector and you know, everybody has seen pharmacies and chain stores really take up providing vaccines. There are now better insurance efforts that mean everybody has access to recommended vaccines with no copay, no deductible, as long as they are vaccinated in an in-network provide and there are public insurers that cover the vaccine.

The good thing for 65-year-olds and over is that Medicare coverage is very good for the pneumococcal and the flu vaccine.

Mr. GRIFFITH. Well, I appreciate those answers. Appreciate you all being here.

Mr. Chairman, I appreciate you holding this hearing and I would say that while I was not in the room and I apologize for that I was trying to do a couple of things at the same time. I was listening to some of the testimony earlier and I have some of the same concerns that Ms. DeGette has in regard to egg-produced vaccines. So just note that she is not the only voice up here that is concerned about that issue.

Mrs. BROOKS. Would the gentleman yield the balance of his time?

Mr. GRIFFITH. Yes.

Mrs. BROOKS. Thank you. I have a very brief question, a follow-up question for Dr. Robinson. Can you share with me what is the status of the 2005 HHS pandemic preparedness plan and has it been updated since it was issued by Bush administration?

Dr. ROBINSON. Yes, fortunately, the Department is in a very strident effort right now to update that. We expect that it will be available at the end of next summer. The entire Department represented here and others are actively working on that, using that pandemic plan and the National Strategic Plan as a base and then go forward with that and have combined a number of different efforts that have been going on for a number of years to funnel it towards that plan.

Mrs. BROOKS. Thank you. I yield back.

Mr. MURPHY. Ms. DeGette, I am going to re-recognize you for followup.

Ms. DEGETTE. Thank you, Mr. Chairman. I don't really have questions. I just want to say that I recognize that we have come a long way and I appreciate the efforts of all of the agencies, but I am still concerned about some of the market forces that we had discussed during my questioning. I am concerned that those market forces are really keeping us stuck in some old ways of thinking, and I think that probably all of us would like to work with the agencies to figure out how to update that so that we can be in the 21st century. And that is my main goal.

And Mr. Chairman, I really thank you for holding this hearing. I think it is something we should do every year about this same time. And I encourage all of you to continue your good work, both on the seasonal flu vaccinations and readiness and also on the longer-term issues around pandemic flu. Thank you, Mr. Chairman.

Mr. MURPHY. Thank you. I just have a followup to a couple of things that Mr. Griffith and Ms. Brooks said here. So when you are talking about seniors then is the vaccine less effective for seniors? And if so, why?

Dr. SCHUCHAT. Many vaccines are less effective in seniors than in younger people. The influenza vaccine is often less effective in seniors. There have been a lot of efforts to try to overcome that. We think about it as senescence of the immune system and it is particularly worse in the very elderly. So both influenza vaccines and pneumococcal vaccines work less well in the elderly than they work in younger populations. That said, getting vaccinated is the

best way to protect yourself. And so we recommend everybody 65 and over be vaccinated against the pneumonia with the pneumococcal vaccines. And we recommend everybody, 6 months and over get an annual flu vaccination.

Mr. MURPHY. So finally, I would ask each person is the flu vaccine less effective against H3N2 flu strain compared to other strains targeted by the vaccine? Does anybody have any comments on that?

Dr. SCHUCHAT. The review of vaccine effectiveness data from the past decade provides us some clues that on average the vaccines that we are using are less effective against the H3N2 strains, even in years where there is a reasonably good match. On the other hand, we still see efficacy most years, not all, but most years and we strongly recommend people get vaccinated.

At this time of year, we don't know what strain is going to dominate and how well the vaccine is going to work, but we do know that being vaccinated protects you substantially compared to not being vaccinated.

Mr. MURPHY. Thank you. Anyone else want to comment on that? Then let me also echo what some of the Members have said here, because these hearings have been going on for a decade. And we want to see that your agencies are updating also their scientific approach to this, not only trying to guess what the next nasty bug is going to be coming around, and trying to predict that, develop a vaccine, and find out that it mutates faster than we can manufacture them.

But do we need different scientific designs on that?

I hope that when we approach this again in the coming months, first of all, I hope that this is more accurate for this year's vaccine. We hope people get it. We hope people eat right, rest right, and exercise so the person won't work on a person that is weak and sickly anyways or less effective. But we want to be able to come back and say lessons learned, lessons applied much more effective and I thank you all for your testimony today. We really appreciate you being here today, and with that—I might want to add here that I ask unanimous that the correspondence between the committee and HHS, CDC, BARDA, NIH, as well as HHS's May 6th memorandum be introduced into the record.

[The information appears at the conclusion of the hearing.]

Mr. MURPHY. And without objection, the documents be entered into the record.

We ask also that, as you receive questions, you respond back to the committee quickly. Members have 10 business days to submit those questions to the record. And with that, I now adjourn this hearing. Thank you.

[Whereupon, at 12:06 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

PREPARED STATEMENT OF HON. FRED UPTON

Continuing our longstanding efforts on flu preparedness, today's discussion follows up our hearing last February that focused on a very harsh flu season with a mismatched vaccine that had an overall effectiveness of only 19 percent. Although the official statistics for last flu season are not available yet, in such a severe flu season, we would see up to 50,000 deaths, more than 400,000 hospitalizations, and an economic burden of about $87 billion. I, like others on this subcommittee, ex-

pressed my belief at that February hearing that we can—and must—do better in addressing this major public health threat to protect folks in Michigan and across the country.

Earlier this year, the World Health Organization (WHO) warned that flu strains have grown increasingly complex, and have been distributed broadly across the globe. This diversity and geographic distribution is unprecedented since the advent of modern tools for flu virus detection and analysis. Last year's poorly matched seasonal flu vaccine and the bird flu H5 viruses that killed millions of birds in the Midwestern U.S. earlier this year are the most recent examples of this complexity. The WHO cautioned that the consequences of so many flu viruses emerging are "unpredictable" and "potentially ominous."

Since the February hearing, our committee has been conducting bipartisan oversight into how to improve the U.S. public health response on seasonal flu and the adequacy of HHS efforts in monitoring the impacts of the bird flu outbreak. I am pleased to learn that Secretary Burwell and HHS leadership have made the response to seasonal flu vaccine mismatch a greater priority, and that HHS has been working throughout the year on various actions to improve seasonal flu preparedness. I look forward to discussing the details about these actions, and how they are expected to improve the response.

Flu is a major public health challenge. The actions from HHS and its agencies are a good start. We recognize, however, that much work needs to be done. We will also be asking questions to make sure our preparedness efforts are addressing all potential problems and gaps. Our discussion today is aimed at being constructive, and detailing ways we can work with HHS to improve our flu response to save thousands of lives.

I appreciate the hard work and dedication of the folks at HHS, the CDC, the FDA, BARDA, and the NIH on flu preparedness. I look forward to today's testimony, and continuing the work to improve the U.S. flu response. Our collective efforts are about keeping Americans healthy during the flu season. From babies who are 6 months old to the elderly, and everyone in between, folks in Michigan and across the country should have the peace of mind and faith that their flu shot will keep them healthy. Our bipartisan work continues.

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON ENERGY AND COMMERCE

November 17, 2015

TO: Members, Subcommittee on Oversight and Investigations

FROM: Committee Majority Staff

RE: Hearing on "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?"

The Subcommittee on Oversight and Investigations will hold a hearing on Thursday, November 19, 2015, at 10:00 a.m. in 2322 Rayburn House Office Building, entitled "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?" This hearing follows up on the Subcommittee's hearing on February 3, 2015, that examined the U.S. public health response to seasonal influenza. The Subcommittee will be examining the lessons learned from last season's influenza vaccine mismatch to the predominant influenza virus that resulted in more deaths and hospitalizations because of the vaccine's lower than usual effectiveness. The purpose of the hearing is to better understand the key challenges in flu vaccine development that the U.S. public health agencies seek to address and review recommended actions to improve seasonal influenza preparedness.

I. WITNESSES

Dr. Anne Schuchat
Principal Deputy Director
Centers for Disease Control and Prevention (CDC)

- *Makes recommendations on who should be vaccinated, tracks the spread of influenza and vaccination rates, and disseminates public health messages encouraging vaccination and other protective measures, such as hand-washing.*

Dr. Karen Midthun
Director, Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

- *Selects the influenza strains to include in the annual influenza vaccines and for licensing vaccines.*

Dr. Robin Robinson
Director
Biomedical Advanced Research and Development Authority (BARDA)
Office of the Assistant Secretary for Preparedness and Response

- *Funds the research and development of influenza vaccines.*

Dr. Carole Heilman
Director
National Institute of Allergy and Infectious Diseases (NIAID)

Division of Microbiology and Infectious Diseases
National Institutes of Health (NIH)
- *Conducts and supports research on influenza.*

II. BACKGROUND

A. The Influenza Threat

Influenza is a leading cause of death in the U.S. Influenza is a contagious respiratory illness caused by varying virus strains and can range in severity from mild to lethal. In both its seasonal and pandemic forms, influenza is an ongoing public health concern.[1] In the northern hemisphere, seasonal influenza may begin as early as August and generally diminishes by April. An average of 62 million Americans —about 20 percent of the U.S. population —get the flu each year.

Influenza is considered one of the leading causes of death in the U.S., especially in a severe season. Based on 2010 data, CDC has estimated that the number of deaths annually caused by influenza and pneumonia was 53,826.[2]

According to CDC estimates for the 1976-2006 time period, seasonal influenza has been associated with as few as 3,000 and up to almost 50,000 deaths each year in the U.S. On average each year, more than 36,000 individuals die and an estimated 226,000 are hospitalized from influenza and related complications.[3] A study published in 2007 estimated that more than $10 billion is spent annually in direct medical costs for hospitalizations and outpatient visits from seasonal influenza-related complications[4] and there is an overall annual economic burden of $87.1 billion.[5]

Detailed published estimates of influenza-attributable deaths by age, type, and subtype have not been updated by the CDC for seasons beyond the 2006-2007 influenza season.[6] CDC does not know exactly how many people die from seasonal flu each year. The reasons for this include: states are not required to report individual seasonal flu cases or deaths of people older than 18 years of age to CDC; many influenza-related deaths, such as from pneumonia, may not include any mention of influenza on the death certificate; many patients (especially the elderly)

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[1] Seasonal flu is an outbreak that follows predicable seasonal patterns. Pandemic flu is a worldwide outbreak of a new form of flu virus, which can spread easily from person to person because they have no immunity.
[2] CDC FastStats, Death and Mortality, *available at* http://www.cdc.gov/nchs/fastats/deaths.htm.
[3] In a January 28, 2015 phone briefing with staff, the Acting Director of the CDC's Influenza Division stated the estimates for hospitalizations could be as high as 400,000.
[4] CDC Congressional Justification FY 2015, *available at* http://www.cdc.gov/fmo/topic/Budget%20Information/appropriations_budget_form_pdf/FY2015_CJ_CDC_FINAL.pdf.
[5] N.A. Molinari, et al., 25 Vaccine 5086 (2007).
[6] Gonçalo Matias, Robert Taylor, François Haguinet, Cynthia Schuck-Paim, Roger Lustig and Vivek Shinde, "Estimates of mortality attributable to influenza and RSV in the United States during 1997–2009 by influenza type or subtype, age, cause of death, and risk status," Influenza Journal 507 (June 27, 2014), *available at* http://onlinelibrary.wiley.com/doi/10.1111/irv.12258/full. However, CDC has indicated to staff that there is an update that covers the 2005-2014 period that will be released shortly.

may die from pneumonia unrelated to influenza, so figuring out which cases to include in an analysis can be difficult; most people who die from seasonal flu-related complications are not tested for flu or they seek medical care when flu can no longer be detected.

Given the difficulties on getting exact numbers of flu-related deaths, researchers have turned to a variety of modeling techniques to estimate deaths. One retrospective database analysis, which estimated influenza deaths in the U.S. by analyzing data for 12 influenza seasons (1997-2009), found that influenza deaths were highest in older and high-risk individuals. In terms of deaths from influenza and pneumonia, CDC statistics[7] show that between 1999 and 2011 there were on average some 20 deaths each year (high of 23 and low of 17) per 100,000 of the US population. Other recent data and CDC statements indicate there is no reason to think that there has been any major change between 2011 and 2014. Over the 1999-2011 period the death rate per 100,000 was 35 for the group aged 65-74; 140 for the group aged 75-84; and 600 for the 85+ group. There was also a higher than average death rate for infants of less than 1 year. Adults between 20 and 50 obviously had much lower rates. The figures do not distinguish between those who had received a vaccine shot in a particular year and those who had not; nor any who had a history of previous flu shots. The greatest burden of influenza disease occurs in persons aged 65 years and older despite achieving an immunization rate of 65 to 70 percent in this population.

It is important to note that the impact of seasonal flu can be as serious as impact of pandemic flu. Seasonal influenza has significant health and economic impacts, with a cumulative impact as serious as a pandemic. According to the World Health Organization (WHO), annual seasonal influenza epidemics result in about 3 million to 5 million cases of severe illness and about 250,000 to 500,000 deaths worldwide, which is likely an underestimation. As noted in a 2012 report by the Center for Infectious Disease Research & Policy, "[T]hese figures indicate that the cumulative health impact of seasonal influenza over the last century rivals the potentially explosive, but time-limited, impact of the four pandemics of the past 100 years."[8]

B. Influenza Strains and Detection

The influenza virus is a single-stranded RNA virus.[9] However, there are three types of influenza virus (A, B, and C) that are distinguished by their different main nucleoproteins.[10] Although all three types of influenza virus have the capacity to infect humans, types A and B are the deadliest. In particular, influenza A H3N2 virus poses the greatest concern. When the H3N2 flu viruses are predominant, it tends to cause more severe illness and hospitalization among the

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[7] www.cdc.gov/nchs/faststats/deaths.htm

[8] Center for Infectious Disease Research & Policy, University of Minnesota, The Compelling Need for Game-Changing Influenza Vaccines: An Analysis of the Influenza Vaccine Enterprise and Recommendations for the Future, 11 (October 2012).

[9] B. Tesfayesus, et al., "Influenza: How serious is it?" Clinical Advisor (November 9, 2015) http://www.clinicaladvisor.com/influenza-how-serious-is-it/printarticle/452733/

[10] http://www.cdc.gov/flu/about/viruses/types.htm. In addition, each of these viruses are further identified by two proteins: hemagglutinin (H) and neuraminidase (N). These proteins play a key role in causing the flu virus by neutralizing antibodies.

elderly. According to one study, the H3N2 A strain accounted for a seasonal average of 71 percent influenza-attributable deaths compared to the other strains.[11]

Recently, the influenza strains have grown increasingly complex and have been distributed more broadly across the globe. In February 2015, the WHO noted, "The diversity and geographical distribution of influenza viruses currently circulating in wild and domestic birds are unprecedented since the advent of modern tools for virus detection and characterization. The world needs to be concerned."[12] In 2015, so many new types of flu, including highly infectious strains, have emerged that public health officials around the world are racing to keep up with the viruses and spot the dangers they may pose.[13] For example, new influenza A viruses are constantly emerging from animal reservoirs, and there has been a tenfold increase in the number of human infections with different novel influenza A viruses since the 1990s.[14]

The news of this array of genetic forms of influenzas is partly a result of improved surveillance measures.[15] However, many scientists believe that the pace of evolution in influenza is speeding up because of human movement and trade along the Asian flyway, giving more opportunities for various types of flu to comingle, jumble their RNA genetic material, and form novel strains.[16] This in turn is making it harder for scientists to predict which forms of influenza are likely to hit human populations, accurately predict what type of vaccine is likely to be effective for that season, and anticipate the movement of flu viruses from wild birds to domestic fowl, fowl to humans, humans to swine, and swine back to humans. The consequences from the emergence of so many novel viruses "for animal and human health are unpredictable yet potentially ominous."[17]

The speed in which influenza can be detected is a key concern. While the complexity and number of flu viruses is increasing, antiquated testing may delay detection of mutations in certain seasonal influenza viruses. Antigenic testing for strain selection is still based on the HAI assay, which was developed in the 1940s. In 2011, a WHO Conference report acknowledged this assay had performance issues in recognizing emerging changes in the H3N2 viruses.[18] Poor performance of these H3N2 strains in the HAI assay may delay recognition that a new antigenic variant of H3N2 is emerging.

C. The Seasonal Flu Vaccine: Development and Effectiveness

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[11] Matias, *supra*, note 4.
[12] WHO, "Warning signals from the volatile world of influenza viruses," February 2015. http://www.who.int/influenza/publications/warningsignals201502/en/
[13] L. Garrett, The Year of the Flu, February 4, 2015. http://www.cfr.org/public-health-threats-and-pandemics/year-flu/p36079
[14] Institute of Medicine, Rapid Medical Countermeasure Response to Infectious Diseases, Workshop Summary (2015)(referencing presentation by Dr. Jacqueline Katz, deputy director (acting) of the Influenza Division at the CDC.
[15] Id.
[16] L. Garrett, note 9.
[17] WHO, note 8.
[18] WHO Conference Report, Strengthening the influenza vaccine virus selection and development process, Outcome of the 2nd WHO Informal Consultation for Improving Influenza Vaccine Virus Selection held at the Centre International de Conferences (CICG) Geneva, Switzerland, 7 to 9 December 2011, 31 Vaccine 3209, 3213 (2013).

The primary method for preventing influenza is annual vaccination. CDC recommends annual vaccinations for everyone aged 6 months or older. According to a CDC study published in the journal *Vaccine*, the seasonal flu vaccine prevented more than 40,000 flu-associated deaths in the United States during a nine-year period, from 2005-2006 through 2013-2014.[19]

For the 2011-2012 season, about 42 percent of Americans aged 6 months and over were vaccinated.[20] Data from the 2012-2013 season showed that 45 percent of Americans 6 months or older got vaccinated.[21] For 2013-2014 season, the overall vaccination rate was 46 percent.[22] The estimate for this season as of November 2014 was 46.2 percent. According to the CDC FY 2015 Congressional Justification, the CDC set a performance measure for the long term objective to increase the proportion of adults (18 and older) who are vaccinated annually against influenza. In FY 2013, the CDC set the target at 42 percent but that target was not met. The FY 2014 target was 50 percent and the goal for FY 2015 was 53 percent.

HHS has set a goal for states to vaccinate 70 percent of their population as part of the Healthy People 2020 initiative. According to experts, vaccination rates need to be generally above 70 percent for "herd immunity" effects – which limit the spread and protect those without immunity – to become apparent. If all seniors received a newly available high-dose version of the flu shot, flu cases among this high-risk population could drop 25 percent.[23]

Because circulating influenza virus strains change, a new vaccine is produced and administered each year to protect against strains expected to be most prevalent that year. "Influenza is a very challenging virus in that its surface proteins change constantly to evade both our immune systems and vaccines. As a result of these changes, in most years, at least one of the strains in the vaccine must be changed to keep up with changes in the circulating virus."[24] Each year, public health experts, including those from FDA, the WHO, and CDC, study influenza virus samples and global disease patterns to identify virus strains likely to cause the most illness during the upcoming season. Based on that information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee (VRBAC), FDA selects the strains for inclusion in the annual influenza virus – two strains of influenza type A and one strain of influenza type B – to include in the annual influenza vaccine.[25] Because of the lead time

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[19] I. Foppa, et al., "Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14, 33 Vaccine 3003 (March 23, 2015), www.sciencedirect.com/science/article/pii/S0264410X15002315.

[20] Written testimony of Dr. Thomas Frieden, CDC Director, before the House Energy and Commerce Subcommittee on Oversight and Investigations, February 13, 2013 at 8 (indicating that the rate was 52 percent but that was for the subgroup of Americans aged 6 months to 17).

[21] Flu Vaccination Coverage, United States, 2012-13 Influenza Season, http://www.cdc.gov/flu/fluvaxview/coverage-1213estimates.htm.

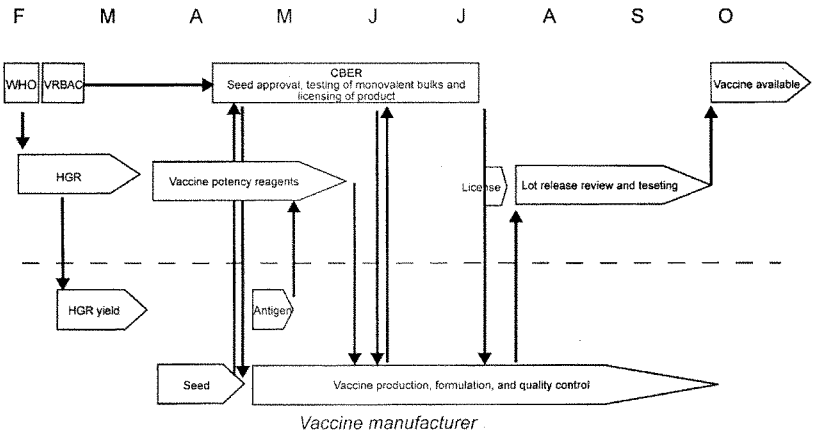
[22] 2010-11 through 2013-14 State, Regional, and National Vaccination Trend Report, http://www.cdc.gov/flu/fluvaxview/reports/reporti1314/trends/index.htm.

[23] R. Roos, "Large trials finds high-dose flu shot beneficial for seniors," CIDRAP, August 13, 2014, http://www.cidrap.umn.edu/news-perspective/2014/08/large-trial-finds-high-dose-flu-shot-beneficial-seniors.

[24] Statement of Jesse Goodman, M.D., MPH, Chief Scientist, FDA, Hearing before the House Energy and Commerce Subcommittee on Oversight and Investigations, "Influenza: Perspective on Current Season and Update on Preparedness, February 13, 2013.

[25] This is the trivalent vaccine. Since 2013, there has also been a quadrivalent vaccine available that includes an additional B strain.

needed for manufacturing flu vaccine, the decisions on strain selection need to be made usually by the end of February for vaccine to be available later in the year for the flu season in the U.S.



Above is a graphic illustration[26] of the annual timeline for the U.S. vaccine production process.

For last year's flu season, there were about 150 million doses of flu vaccine available annually in the U.S., with about 140 million doses from egg-based manufacturing and 10 million doses from cell- and recombinant-based. The estimated lead times to first dose for each type of manufacturing are as follows: egg-based, 22-24 weeks; cell-based, 16-17 weeks; and recombinant, 12-15 weeks. For this year's flu season, HHS subject matter experts advised committee staff last week that there would be a record supply of 170 million doses of flu vaccine. Although there was no specific estimate of the number of egg-based doses, experts expected that more than 90 percent of the vaccine supply would be egg-based.

Seasonal flu vaccination typically has an effectiveness[27] rate in the range of 50-60 percent.[28] Seasonal flu vaccine effectiveness studies show a low effectiveness rate of 10 percent

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[26] Slide 8 from Novartis briefing to Members of the Subcommittee, January 27, 2015 (on file with Committee). HGR refers to high-growth reassortants. The viruses that are made by WHO (in eggs) as the foundation for the year's vaccine. They have surface proteins of the recommended flu strain, but the viral core of strains that are easy to grow.

[27] By effectiveness, CDC means the rate at which the vaccine prevents a person from going to the doctor to seek treatment. Thus, in a population of 100 unvaccinated people exposed to the flu virus, the CDC would expect about 10 to seek treatment. In a population of 100 vaccinated people exposed to the flu virus, the CDC would expect 4 people to seek treatment, but would prevent 6 from going to the doctor.

[28] By way of comparison, effectiveness rates for other vaccines such as for measles are about 95 percent. The comparison highlights the unique challenge posed by the constantly changing flu viruses.

(in high-risk populations) for the 2004-2005 season with a high rate of 60 percent (general population) in the 2010-2011 season. Vaccination, even with effectiveness of about 60 percent, has been shown to reduce flu-related illness, antibiotic use, time lost from work, hospitalizations, and deaths. However, vaccine efficacy was less than 40 percent during 4 out of the past 10 years.[29] A meta-analysis of 60 past studies of flu vaccine effectiveness presented at an infectious disease conference in San Diego last month found only 38 percent effectiveness against the H3N2 influenza virus.[30]

Lower effectiveness may be attributable, in part, to antigenic drift. "Antigenic drift" refers to small changes in the genes of influenza viruses that happen continually over time as the virus replicates.[31] These small genetic changes usually produce viruses that are closely related to one another.[32] While these small genetic changes can accumulate over time, this can lead to viruses that look different to a person's immune system. The antibodies created against older viruses no longer recognize the "newer" virus, and the person can get sick again.[33]

Egg adaptation may also contribute to lower effectiveness of the vaccine. Vaccine effectiveness is generally interpreted in the context of vaccine match/mismatch to circulating strains that have mutated to explain reduced protection. However, in 2014, a study funded by the Canadian Institutes of Health Research, found that during the 2012-2013 flu season the low vaccine effectiveness was related to mutations in the egg-adapted H3N2 vaccine strain rather than antigenic drift in circulating viruses.[34] Although there is no significant antigenic drift in the 2015-2016 strain selection, there are still concerns about the H3N2 strain in this season's vaccine. Publicly available data from the WHO Collaborating Center in the United Kingdom generated in February 2015, prior to the Northern Hemisphere selection, showed that although the mammalian cell-adapted A/Switzerland/9715293/2013 would provide reasonable coverage of recent H3N2 strains, it undergoes a significant antigenic change upon egg adaptation that greatly reduce the coverage. Because eggs are used to propagate the viruses that the WHO sends to U.S. vaccine manufacturers and because most of the influenza vaccine supply is produced in eggs, the mismatch due to egg-adaptation could have an important impact on vaccine match this season, even if there is little antigenic drift.

D. The 2014-2015 Seasonal Influenza Vaccine Mismatch

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[29] Fluview, CDC, Table of Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2015.
[30] S. Zhang, "Scientists Found a Flu Vaccine – Now They Have to Fix It," Wired (October 9, 2015). http://www.wired.com/2015/10/scientists-pinpoint-flu-vaccine-flaw-h3n2/. See also H. Branswell, "Weak link discovered in flu vaccine," STAT, (October 7, 2015) https://www.bostonglobe.com/lifestyle/health-wellness/2015/10/06/researchers-find-weak-link-flu-vaccine/sJrqYQ2eFdbeFEMFXLEViO/story.html.
[31] Response attached to letter from Thomas R. Frieden, MD, MPH, Director of the CDC to The Honorable Fred Upton, Chairman, House Energy and Commerce Committee, et al., April 9, 2015. In contrast, "antigenic shift" is an abrupt, major change in the influenza A viruses that emerge from an animal population. Because the majority of people would have no immunity to the new virus, a much higher population attack rate – the pandemic scenario - would be expected.
[32] Id.
[33] Id.
[34] D. Skowronski, et al., Low 2012-13 Influenza vaccine Effectiveness Associated with Mutation in the Egg-Adapted H3N2 Vaccine Strain Not Antigenic Drift in Circulating Viruses, PLOS (March 25, 2014). http://journals.plos.org/plos.org/plosone/article?id=10.1371/journal.pone0092153

The U.S. experienced a severe flu season in 2014-2015 because that year's vaccine did not protect well against the dominant H3 A strain of influenza, which mutated after the vaccine-production process began for the 2014-2015. Given the lead time needed for manufacturing and regulatory compliance, there was not enough time to modify the vaccine and restart the manufacturing.

An analysis of the 2014-2015 seasonal flu vaccine showed only 19 percent effectiveness for the overall U.S. population — much less so for most American adults, with close-to-final statistics demonstrating only 12 percent effectiveness for those 18-49 years old and 14 percent for those 50 years or older. This is the lowest rate since CDC has collected standardized, more accurate data of effectiveness rates in the last four to five years.

The lower effectiveness is due to significant mutations in a key flu strain (the dominant H3N2 A strain) that occurred sometime after the strain selection decision for the U.S. vaccine was made in February and before the onset of this year's flu season in the U.S. This occasionally occurs. For example, CDC stated during a staff briefing that the 1999 seasonal flu vaccine had near zero effectiveness because of drift in the strain from mutations.

CDC first detected the drift of the H3N2 A strain in March 2014, but the drift was at an insignificant level, and not yet considered evidence of a distinctive and meaningful drift. Sometime in May, CDC found that the drift resulted in a 17 percent mismatch, a level of concern but not unambiguous evidence of a significant drift.[35] CDC indicated to staff that a drift in the range of 20 to 30 percent would be considered significant. CDC later confirmed a drift of 36 percent for the summer, but CDC did not find a qualified candidate virus until September. By September 2014, the mismatch was about 50 percent, and a vaccine candidate for the new strain was identified. As a result, the WHO recommended replacing the H3 A strain in the seasonal flu vaccine for the Southern hemisphere. The drift wound up at about a 66 percent mismatch level.

For the 2015-2016 seasonal flu vaccine for the U.S., CDC reported to the Committee that through late May, more than 90 percent of the U.S. influenza viruses tested by CDC were antigenically like or similar to the vaccine viruses.

E. Committee's Continuing Oversight

Following the Subcommittee's hearing on February 3, 2015, bipartisan committee leaders sent letters on March 9, 2015, to the CDC, FDA, NIH, BARDA, and the Secretary of Department

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[35] Whether there was enough drift seen in May 2014 to change the strain selection decision is in dispute. Dr. Andrew T. Pavia, M.D., Professor and chief of the Division of Pediatric Infectious Diseases at the University of Utah School of Medicine and who has served on federal and state advisory committees on vaccine policy and pandemic influenza preparedness, stated: "If we had picked the vaccine strain in May instead of February 2014, we would have picked the correct one. By April or May, there was good evidence of the drifted A/Switzerland strain; it wasn't clear that it was going to be the dominant strain, but there was a pretty good hint and we probably would have chosen differently." Another flu expert, Dr. Gregory A. Poland, M.D., Professor of Medicine and director of the Vaccine Research Group, Mayo Clinic said the current way of predicting the dominant virus of the coming influenza season is outdated and should be improved. L. Brookes, A. Pavia, and G. Poland, "Why Is Influenza So Difficult to Prevent and Treat? Will We See Improvement Any Time Soon?" www.medscape.com (January 23, 2015). http://www.medscape.com/viewarticle/838459_print

of Health and Human Services (HHS). They asked each agency additional questions about the U.S. public health response to last year's flu season, as well as what ways the agencies could improve preparedness for seasonal influenza. On July 31, 2015, bipartisan committee leaders sent another letter to HHS Secretary Sylvia Burwell with additional questions and a request for documents on recommendations or lessons learned from last year's flu season. HHS provided answers to the questions in a September 30, 2015 response. Later, HHS produced a May 6, 2015 memorandum sent to Secretary Burwell on influenza process improvements.

F. Improvements in U.S. Response to Seasonal Influenza

Since the Subcommittee's hearing in February about the 2014-2015 vaccine mismatch, there are indications of seasonal influenza being made a greater priority and getting more attention than in the past. First, the HHS Influenza Risk Management Group, which has primarily met over the last 12 years on pandemic influenza issues, has been including seasonal influenza issues on the agenda during meetings in 2015. Second, HHS Secretary Sylvia Burwell, through her counselors, requested that HHS experts recommend actions to mitigate the seasonal influenza mismatch problem. Third, on May 6, 2015, a memorandum of influenza process improvements was sent to Secretary Burwell. Finally, earlier this month, HHS held a table top exercise with HHS agencies and vaccine manufacturers, to solicit their individual opinions. The exercise outcome is expected to inform an HHS action plan for rapid development and manufacturing of a revised seasonal influenza vaccine as a strain change or a separate monovalent vaccine.

Here are some of the key actions being taken to improve seasonal flu preparedness:

- *Technological improvements.* Vaccine manufacturers are in the process of adopting several process improvements for pandemic vaccine. HHS anticipates and will ask that these improvements also be applied to seasonal influenza vaccine manufacturing. Application of these improvements to seasonal influenza could save four to six weeks in the manufacturing and formulation process. If successful, strain selection decisions could be made with surveillance information closer to the beginning of the influenza season.

- *Use of the Influenza Risk Assessment Tool (IRAT).* HHS uses the IRAT for decisions to make limited amounts of vaccine in response to emerging, potentially-pandemic strains. The HHS Influenza Risk Management Group, using the IRAT as a model, is working to develop a risk assessment method within the next 15 months to guide recommendations about whether to change seasonal vaccine strain composition between the WHO recommendation and June.

- *Monovalent rescue vaccine.* Recent discussions at the Flu Risk Management Meeting (FRMM), which is coordinated by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), have included considerations to determine under that circumstances a monovalent rescue vaccine would be pursued due to a drifted seasonal influenza strain. Factors that could impact that decision include

manufacturing capabilities and disease severity. In 1986, FDA approved a monovalent influenza vaccine to supplement the trivalent influenza vaccine to address a drift of the H1N1 strain.[36] Approximately 7 million doses of the 1986 monovalent vaccine were manufactured or distributed late in 1986.[37]

- *Late season change to tri- or quadrivalent vaccine.* HHS has taken a series of steps to increase the probability that a late season change to tri- or quadrivalent vaccine could be made. These changes would also enable faster production of a monovalent vaccine should it be needed. Some of these key steps include: FDA making more potency assay reagents to facilitate the production of new vaccines, CDC (with WHO) helping improve availability of additional vaccine viruses, CDC (with WHO) enhancing global surveillance of circulating human and avian influenza viruses.

- *Increased communication.* More frequent and comprehensive communication with HHS leadership and FDA has been implemented, and FDA has done likewise with the Chair of its Vaccines and Related Biological Products Advisory.

- *Antivirals and other strategies.* As during the 2014-2015 influenza season, CDC emphasizes the use of antiviral medications as a "second line of defense," promotes pneumococcal vaccination for seniors to help mitigate the complications of flu in the elderly, and stresses the importance of everyday preventive actions like covering coughs, social distancing, and frequent hand washing.

G. Pandemic Influenza

As noted in Dr. Robin Robinson's February 3, 2015, testimony before the Subcommittee, preparedness and response plans for seasonal and pandemic influenza "are inextricably interwoven; what we do in one area directly affects what we do in the other." Thus, pandemic flu preparedness should be noted in the context of the hearing.

An influenza pandemic can occur when a novel, non-human influenza virus becomes able to spread efficiently through human-to-human transmission. The viruses circulate in birds or other animals, so there is little to no immunity against these viruses among people. Examples include the avian "bird flu" influenzas H5N1 and H7N9. The Centers for Disease Control and Prevention refers to influenza viruses that have the potential to cause a pandemic as "influenza viruses with pandemic potential."[38]

U.S. public health agencies rely on many of the same tools to identify and track seasonal influenza viruses and influenza viruses with pandemic potential. These preparedness efforts include "ongoing surveillance of human and animal influenza viruses, risk assessments of

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[36] Letter from Thomas A. Kraus, FDA Associate Commissioner for Legislation to The Honorable Fred Upton, Chairman, House Energy and Commerce Committee, et al., April 8, 2015.
[37] CDC , 37 CDC Morbidity and Mortality Weekly Report 469 (August 12, 1988).
[38] CDC Resources for Pandemic Flu, Centers for Disease Control and Prevention, http://www.cdc.gov/flu/pandemic-resources/ (last visited Nov. 13, 2015).

influenza viruses with pandemic potential, and the development and improvement of preparedness tools" for public health practitioners.[39]

The HHS Influenza Risk Management Group, comprised of officials from BARDA, HHS Office of the Assistant Secretary for Health (OASH), NIH, CDC, and FDA, also meets monthly to discuss updates on seasonal and pandemic influenza issues, including preparedness issues.

HHS maintains three influenza preparedness documents—the 2005 *Pandemic Influenza Plan*, the 2009 *H1N1 Influenza Improvement Plan*, and the Pandemic Annex to the HHS All-Hazards Plan. The 2005 *Pandemic Influenza Plan* acts "as a blueprint for all HHS pandemic influenza preparedness planning and response activities."[40] The 2009 *H1N1 Influenza Plan*, released in 2012, communicated "HHS' priorities for modifying and updating the prior 2005 *HHS Pandemic Influenza Plan*, informed by lessons learned from the 2009 H1N1" influenza pandemic.[41] The Pandemic Annex to the HHS All-Hazards Plan is one of multiple threat-specific annexes that augment the overall plan.[42] While HHS is currently updating all three plans, the Department does not expect the revised plans to be complete until 2016.

III. ISSUES

The following issues will be examined at the hearing:

- What were the lessons learned from the last season's flu vaccine mismatch?
- How effective are the steps that HHS is taking to improve seasonal influenza preparedness in addressing the lessons learned?
- How can better and more effective flu vaccines be made?
- What communications or guidance would be effective in helping increase the use of antiviral medications and reduce the use of antibiotics in the treatment for influenza?
- What research needs to be done to determine whether a low level of effectiveness of a seasonal flu vaccine could be substantially increased if the vaccine was adjuvanted?[43]

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[39] CDC Resources for Pandemic Flu, Centers for Disease Control and Prevention, http://www.cdc.gov/flu/pandemic-resources/ (last visited Nov. 13, 2015).
[40] U.S. Dep't of Health & Human Serv., *HHS Pandemic Influenza Plan* 2 (Nov. 2005), *available at* http://www.flu.gov/planning-preparedness/federal/hhspandemicinfluenzaplan.pdf.
[41] U.S. Dep't of Health & Human Serv., 2009 H1N1 Influenza Improvement Plan 3 (May 29, 2012), *available at* http://www.phe.gov/Preparedness/mcm/h1n1-retrospective/Documents/2009-h1n1-improvementplan.pdf.
[42] Letter from Dr. Nicole Lurie, Assistant Sec'y for Preparedness & Response, U.S. Dep't of Health & Human Serv., to Hon. Fred Upton, Chairman, H. Comm. on Energy & Commerce (July 31, 2015).
[43] No adjuvanted seasonal influenza vaccine has ever been licensed in the U.S. to date. Dr. Andrew Pavia stated that with an adjuvanted vaccine "we probably could have made the mistake we made [in the 2014-15 flu] year and instead of efficacy declining from 65 percent to 23 percent, it might have only declined to 40-50 percent." Brookes, et al., supra note 16.

IV. STAFF CONTACTS

If you have any questions regarding the hearing, please contact Charles Ingebretson, Alan Slobodin, Jennifer Barblan, or Brittany Havens at (202) 225-2927.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

April 27, 2015

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, DC 20515

Dear Chairman Murphy and Representative DeGette:

Thank you for your March 9, 2015, letter regarding the U.S. public health response to seasonal influenza. I am pleased to respond to your questions on behalf of Secretary Burwell.

1. **Please list the authorities that are available to HHS to respond to seasonal influenza drifted strains. What criteria would be used by HHS in using such authorities?**

   Answer: The statutory authorities for research and development, licensing, administration and use of vaccines are the same regardless of the influenza strain and whether or not there are drifted strains. The Department of Health and Human Services (HHS) has authorities under the Public Health Service Act (PHS) to conduct research, development, testing, and distribution of seasonal influenza vaccines and to coordinate with State and local quarantine and communicable disease control activities. See, for example, research and development authorities under sections 301 and 319L of the PHS Act (42 U.S.C. 241 and 247d-7e); coordination of vaccine research, development, testing, licensing, production, distribution and evaluation under title XXI of the PHS Act (42 U.S.C. 300aa-1 – 300aa-6); and control of communicable disease authorities under sections 311, 361, and 362 of the PHS Act (42 U.S.C. 243, 264, 265). These and other authorities under the PHS Act support seasonal influenza vaccine programs and communicable disease control activities of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response, and the National Vaccine Program. HHS also has authorities, delegated to the Food and Drug Administration (FDA), to license vaccines or approve them for investigational use under section 351 of the PHS Act (42 U.S.C. 262) or

authorize them for emergency use under section 564 of the Federal Food, Drug, and Cosmetic (FFD &C) Act. (21 U.S.C. 360bbb-3).

2. **Would using an adjuvant in a seasonal flu vaccine to boost effectiveness against a drifted strain require emergency use authority? If not, what authority would be needed?**

   Answer: If FDA receives a license application for a seasonal influenza vaccine containing an adjuvant that is shown to be safe and effective, then FDA can license the vaccine. In addition, as described further below, FDA can use its expanded access and emergency use authorization authorities to allow use of an unlicensed vaccine.

   Adjuvants are an ingredient in a number of vaccines against other bacterial and viral pathogens, and are being investigated for use in seasonal influenza vaccines. The purpose of formulating vaccines with adjuvants is to increase the immune response to the vaccine. This may allow a decrease in antigen dose, the provision of broader efficacy, or both.

   No U.S.-licensed seasonal influenza vaccine includes an adjuvant. Studies of investigational seasonal and pandemic influenza vaccines containing various adjuvants have been conducted. Studies include, but are not limited to, whether use of adjuvanted seasonal influenza vaccine induces a higher immune response to influenza strains included in the vaccine as well as a response to circulating influenza strains that are not included in the vaccine. FDA has approved an adjuvanted H5N1 vaccine for pandemic use, and is always willing to work with sponsors who are developing adjuvanted seasonal influenza vaccines for potential licensure.

   While the use of adjuvants in seasonal influenza vaccines is promising, the use of an unlicensed vaccine for the prevention of infection by a drifted strain of influenza under Emergency Use Authorization would require a declaration that circumstances justify such an authorization, while use under Expanded Access would require a determination that there is no comparable or satisfactory alternative therapy. In each case, to support such use, FDA would need to determine that the potential benefits outweigh the potential risks based on the available data.

3. **Does HHS believe that a legislative clarification of public health emergency authority would be helpful?**

   Answer: The Department believes that its current authorities are adequate for managing the public health response to the seasonal flu in the U.S.

4. **What databases does HHS have that could be used to track the effectiveness of influenza vaccines?**

Answer: CDC conducts studies to measure the benefits of seasonal flu vaccination each flu season to help determine how well flu vaccines are working. These vaccine effectiveness (VE) studies regularly assess and confirm the value of flu vaccination as a public health intervention. Study results of VE can vary based on study design, outcome(s) measured, population studied and the season in which the flu vaccine was studied.

Through the U.S. Flu VE Network, CDC has been working with researchers at universities and hospitals since the 2003-2004 flu season to estimate how well flu vaccine works through observational studies using laboratory-confirmed flu as the outcome. The U.S. Flu VE Network currently consists of five study sites across the U.S. that measure the flu vaccine's effectiveness at preventing outpatient medical visits due to laboratory-confirmed influenza. CDC's observational studies at U.S. Flu VE Network sites measure outpatient visits for laboratory-confirmed influenza infections using a highly-accurate lab test called rRT-PCR to verify the outcome. These studies compare the odds of vaccination among outpatients with acute respiratory illness and laboratory-confirmed influenza infection to the odds of vaccination among outpatients with acute respiratory illness who test negative for influenza infection. More information on the VE Network visit this link: http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm.

5. **What steps is HHS taking to obtain effectiveness information on the influenza vaccines that HHS purchases?**

Answer: Currently, HHS/CDC purchases and distributes approximately 10-15% of the total seasonal flu vaccines available in the United States each year through CDC's Vaccines for Children and Section 317 Immunization Programs. CDC solicits contracts for all products licensed for use in the United States each flu season and awards contracts to multiple vendors. The products purchased by HHS/CDC are generally the same as those available to the private sector, and therefore the findings from the U.S. Flu VE Network are relevant to the vaccines purchased by HHS as well as those purchased by the private sector.

In the event of pandemic influenza emergency, we expect that the U.S. government would purchase and distribute pandemic influenza vaccines. We are prepared to estimate pandemic vaccine effectiveness with the Pandemic VE Network (consisting of the current network supplemented by several additional sites to increase sample size). HHS/BARDA also supports field effectiveness studies with industry partners for pandemic influenza vaccines as a FDA-licensure commitment.

I hope that this information is helpful to you. Thank you for your continued commitment to public health preparedness.

Cc: ASPR

FDA Commissioner

CDC Director

Sincerely,

[redacted]

Jim R. Esquea
Assistant Secretary
for Legislation

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

April 9, 2015

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
House Energy and Commerce Committee
U.S. House of Representatives
Washington, DC 20515

Dear Chairman Murphy:

Thank you for your letter of March 9, 2015, concerning the House Energy and Commerce Committee's interest in additional information on the public health response to seasonal influenza.

I appreciate the opportunity to provide responses to your recent questions in the enclosed document. We also welcome this chance to share a recent Centers for Disease Control and Prevention (CDC) study, published in the journal *Vaccine*, that shows the seasonal flu vaccine prevented more than 40,000 flu-associated deaths in the United States during a nine-year period, from 2005-2006 through 2013-2014. This estimate represents an almost one-quarter (22%) reduction in the deaths that would have occurred in the absence of flu vaccination during that time. CDC has estimated previously that seasonal flu-associated deaths in the United States range between 3,000 and 49,000 people each year.

To conduct the study, researchers applied statistical modeling with U.S. age-group specific estimates of flu-associated excess deaths, monthly flu vaccination coverage estimates, and summary seasonal flu vaccine effectiveness estimates. Overall, the findings from the study continue to support the benefits of flu vaccination. They suggest that increased flu vaccination coverage and increased flu vaccine effectiveness would help to prevent more flu-associated deaths. The article is available on the *Vaccine* journal website at www.sciencedirect.com/science/article/pii/S0264410X15002315.

Again, thank you for your interest and support of public health-related issues. Should you have additional questions, please contact Randy Katsoyannis in the CDC Washington Office at mkatsoyannis@cdc.gov.

Sincerely,

[redacted]

Thomas R. Frieden, MD, MPH
Director, CDC

Enclosure

cc: The Honorable Fred Upton
The Honorable Frank Pallone

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

April 9, 2015

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations
House Energy and Commerce Committee
U.S. House of Representatives
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Again, thank you for your interest and support of public health-related issues. Should you have additional questions, please contact Randy Katsoyannis in the CDC Washington Office at nkatsoyannis@cdc.gov.

Sincerely,

[redacted]

Thomas R. Frieden, MD, MPH
Director, CDC

Enclosure

Dr. Thomas Frieden Questions for the Record
Committee on Energy and Commerce Subcommittee on Oversight and Investigations
February 3, 2015

1. **If in the future there is another drift of influenza strain and/or a significant risk of a seasonal influenza vaccine mismatch or low effectiveness, under what circumstances would CDC support the production of an off-cycle monovalent seasonal influenza vaccine? What are the criteria for such a decision? Will CDC apply the same rigor used for deciding on a monovalent vaccine to respond to a pandemic as that used for deciding on a monovalent vaccine to respond to a seasonal influenza drifted strain?**

   Answer: The decision to produce an off-season monovalent influenza vaccine may not be the only way to address mismatched seasonal influenza vaccines. A more preferred approach by FDA and others is a strain change that could be accommodated into the standard seasonal influenza vaccine, if feasible based on manufacturing timelines.

   The decision to produce an off-cycle monovalent seasonal influenza vaccine would be made following a recommendation by the FDA's Vaccines and Related Biological Products Advisory Committee and would be based on several factors, including:

   1) Anticipated public health impact of the drifted strain, as determined by the magnitude of antigenic differences, subtype, and antiviral drug susceptibility, among other factors, and the ability of a monovalent vaccine to mitigate that impact;
   2) Probability that drifted strain will become predominant in the coming flu season; and
   3) Stakeholder consensus (including the Biomedical Advanced Research and Development Authority (BARDA), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Advisory Committee on Immunization Practices (ACIP), health care providers, and vaccine manufacturers) on the feasibility of an effective deployment, including capacity to produce enough vaccine in time to achieve high coverage before flu season.

   It is important to understand that the decision to make a monovalent vaccine against a pandemic strain of influenza (antigenic shift) versus to make a supplemental vaccine for the seasonal vaccine in the case of antigenic drift of influenza is based on the risk factors inherently associated with the two different circumstances by which these two types of influenza viruses emerge:

   - "Antigenic drift" refers to small changes in the genes of influenza viruses that happen continually over time as the virus replicates. These small genetic changes

usually produce viruses that are closely related to one another. But these small genetic changes can accumulate over time. This can lead to viruses that look different to a person's immune system; the antibodies created against older viruses no longer recognize the "newer" virus, and the person can get sick again. In this scenario, we would expect the seasonal influenza vaccine to retain some effectiveness against a drifted strain of influenza viruses. In addition, during a drifted season we would expect some level of population immunity due to prior exposures to seasonal influenza viruses. This type of change in the H3N2s circulating in humans was detected in 2014.

- The other type of change is called "antigenic shift." Antigenic shift is an abrupt, major change in the influenza A viruses that emerge from an animal population. This results in new influenza virus proteins that are very different from viruses currently circulating in humans. Because of this, the majority of the population would have no serological immunity to the new (e.g. novel) virus, and we would expect to see a much higher population attack rate. In a pandemic or "shift" scenario, the existing seasonal influenza vaccine would likely have little to no effectiveness at all. Such a "shift" occurred in the spring of 2009, when an H1N1 virus with a new combination of genes emerged to infect people and quickly spread, causing a pandemic.

Pandemic influenza has the potential to be considerably more detrimental to the human population than would a drifted, seasonal influenza virus. In the case of the emergence of a pandemic strain, the decision to produce a monovalent vaccine is clear-cut. In the face of the emergence of a drifted strain an evaluation of risk combined with the logistical considerations regarding how quickly an additional monovalent vaccine could be made available and at what cost become important decision-making considerations. In each scenario ACIP/CDC would use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process to derive recommendations (more information about this process can be found here: http://www.cdc.gov/vaccines/acip/recs/GRADE/about-grade.html).

2. **Did CDC staff between May 1, 2014 and November 1, 2014 ever examine possible responses for the U.S. to the drifted influenza A H3N2 strain? If so, when, and what staff were involved? What were the potential responses considered, and what was the basis for the decision on each of the proposed responses?**

   Answer: CDC's work on the identification and response to the drifted H3N2 strain began prior to May 2014 and involved leadership and staff from CDC's Influenza Division and across the agency. The ability to make vaccine production decisions depends on the development of a suitable candidate vaccine virus. CDC began the process of creating a vaccine candidate virus that was more antigenically similar to the drifted strain in May 2014 (detail below). Prior to that several other events had already taken place:

- In March 2014, CDC detected 5 viruses showing reduced titers with antiserum made against A/Texas/50/2012 (the 2014/15 N. Hemisphere vaccine H3N2 component). On March 28th, then CDC Influenza Division Director and WHO Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza Director Dr. Nancy Cox contacted fellow WHO Collaborating Center directors alerting them to CDC's suspicion of a potential antigenic drift. The purpose was to ask if any countries had detected the same antigenic variants in their surveillance, investigating the presence of geographic spread. This communication facilitated the identification of variant viruses in other regions, **including a virus that was used for generation of candidate vaccine viruses used in vaccine production.**
- In April 2014, CDC expanded genetic analysis of H3N2s to characterize more viruses and gather more data for analysis; at the same time, other WHO collaborating centers began looking specifically for this specific variation in their circulating H3N2 viruses.

In May 2014, CDC began growing a potential candidate vaccine virus strain (A/Palau/6759/2014) that would be more antigenically similar to the drifted virus strain. In June 2014, CDC isolated that candidate vaccine virus strain, and submitted it to New York Medical College (NYMC) for the generation of a high-yield reassortant vaccine virus candidate strain. In July 2014, CDC received a new, egg-grown drifted H3N2 variant A/Switzerland/9715293/2013, and immediately forwarded it to the Influenza reassorting lab at NYMC for creating another potential vaccine candidate virus. In August 2014, CDC performed the preliminary test on A/Palau/6759/2014 to determine if it could qualify as a candidate vaccine virus. Unfortunately, testing indicated that this strain did not have the characteristics to qualify as a vaccine candidate virus. In September 2014, CDC received back a high yielding vaccine candidate virus (A/Switzerland/9715293/2013) from NYMC. CDC then performed its testing on the candidate virus and determined that it qualified as a candidate vaccine virus. On September 26, the WHO recommended the new H3N2 vaccine strain (A/Switzerland/9715293/2013) for inclusion in the Southern Hemisphere vaccine (for 2015).

On October 3rd, CDC published a Morbidity and Mortality Weekly Report (MMWR) entitled "Update: Influenza Activity — United States and Worldwide, May 18–September 20, 2014." It reported that a new H3N2 vaccine strain was selected for inclusion in the Southern Hemisphere vaccine. It also reported that "of the 141 influenza A (H3N2) viruses characterized (78 international and 63 U.S.), 69 (49%) were antigenically similar to A/Texas/50/2012, the influenza A (H3N2) component of the 2014–15 influenza vaccine for the Northern Hemisphere." The influenza season, defined as increased activity above a predetermined threshold, began the end of November 2014. On December 3rd and 4th, after CDC had enough evidence about the viruses that were actually circulating in the United States during the 2014-15 season to determine that the drifted viruses would be

of clinical importance, it released a Health Advisory regarding the potential for circulation of drifted influenza A (H3N2) viruses, and held a press briefing.

3. **What criteria does CDC use to determine that an influenza strain targeted in a current vaccine has significantly drifted and may significantly lower the effectiveness of the current vaccine (i.e. degree of mismatch, trends, locations of mismatch)?**

Answer: There is a difference between vaccine match and vaccine effectiveness. At least two factors play an important role in determining the likelihood that flu vaccine will protect a person from flu illness: the characteristics of the person being vaccinated (such as their age and health); and, the similarity or "match" between the flu viruses the flu vaccine is designed to protect against and the flu viruses spreading in the community. CDC uses multiple laboratory methods in determining if circulating viruses match the vaccine viruses:

1) Antigenic Characterization (analyzing properties of the viruses' surface proteins): Determines how similar the vaccine virus is compared with the circulating viruses using animal sera containing antibodies raised to vaccine virus and representative circulating viruses. More information can be found here: http://www.cdc.gov/flu/professionals/laboratory/antigenic.htm . Using similar methods, human sera from individuals in different age groups vaccinated with the current seasons' vaccine are tested for their ability to react with circulating viruses. In either case, the detection of low reactions with currently circulating viruses characterizes them as antigenically drifted viruses.

2) Genetic Characterization (analyzing the sequence of the viral genes): Genetic analysis of the major surface protein of the virus, the hemagglutinin (HA), which is the target of neutralizing (protective) antibodies, identifies signature amino acid changes are associated with antigenic drift variants.

The relationship between antigenic *match* as determined by these laboratory methods and vaccine *effectiveness* is not straightforward. Even when we identify a drifted strain via the methods above, we cannot predict how well the vaccine will work until the proper epidemiologic field studies are conducted once the influenza season has begun. We have accelerated the pace of these studies so that we get interim results as quickly as possible during the season.

4. **There have been significantly drifted influenza viruses before, four times over the last 20 years according to CDC's testimony. Did the CDC have a contingency plan in case the influenza vaccine was mismatched to a drifted H3N2 A strain? What was the plan, and how was it implemented? Will CDC make any changes in the contingency plan? If so, please identify and explain the changes.**

Answer: In general there are HHS-wide plans for a variety of influenza scenarios. CDC's contingency plan in the event that a drifted strain emerges late (well after the vaccine production and distribution process has begun) is to emphasize the use of other tools in the arsenal to fight the flu. CDC emphasized the use of antiviral medications as a "second line of defense" (to be used in concert with vaccination) and the importance of everyday preventive actions like covering coughs, social distancing and frequent hand washing. CDC feels this is a solid, evidence-based approach and would expect to implement a similar strategy if faced with the same situation. During a "drift" season, CDC continues to recommend influenza vaccination because the vaccine will likely still offer some protection, and it is likely that other influenza subtypes that the vaccine is well matched to will continue to circulate. For example, this year we are seeing a late season predominance of influenza B strains, which are covered by this year's seasonal vaccine. CDC is also increasing contingency plans related to strengthening antiviral treatment practices since these are not yet well implemented but can be of greater importance during years with substantial drift.

5. **Does CDC have a specific public communication strategy when there is a mismatched influenza vaccine in a severe flu season? If so, what is it?**

   Answer: To reduce the substantial burden of influenza on the United States, CDC recommends a three-pronged approach: increasing the number of people vaccinated against influenza, appropriate use of influenza antiviral agents, and promoting respiratory hygiene and cough etiquette.

   Getting a flu vaccine is the best way to prevent influenza illness and protect against its potentially deadly consequences. When a person is sick with flu, however, antiviral flu drugs are a treatment option. During seasons when the availability or effectiveness of one of these interventions is compromised (for example, scenarios where there is insufficient vaccine supply or low vaccine effectiveness), CDC places additional emphasis on the remaining interventions. Thus, while CDC continues to recommend vaccination as an important and still useful preventive measure during a season where there may be or there is reduced vaccine effectiveness, extra emphasis is placed on the use of influenza antiviral drugs for treatment of high risk persons and everyday preventive actions to reduce the transmission of influenza and other respiratory viruses.

   This includes a large communications component, with expanded outreach to clinicians, public health partners, and the public, across multiple channels. While communications efforts are broad-based, as well as targeted, the goal of these efforts is to protect the people who are most vulnerable to serious complications from flu during that given season. For the 2014-2015 season, since surveillance data indicated that H3N2 viruses were predominating and these seasons have been associated with added burden of severe illness among people 65 and older and young children, targeted efforts

emphasized outreach to people in those groups and professionals who care for people in those groups.

This includes:

1. Direct outreach to clinicians (e.g., health alert network messages, clinician outreach and communication activity calls (COCA)).
2. Outreach to clinicians through professional organizations representing those patients at greatest risk (e.g., geriatricians, pediatricians, Infectious Disease Society of America, American Academy of Pediatrics)
3. Outreach to clinicians through mass media (e.g., traditional news media, specialized media like Medscape)
4. Outreach to public health partners (e.g., weekly situation and recommendation updates)
5. Outreach to the public through mass media (e.g., press releases, weekly web updates)

The decision about when to implement this shift in messaging is data driven (e.g., when the data are sufficient to conclude that drifted viruses are predominating and vaccine effectiveness may be reduced). Communications during seasons when vaccine effectiveness may be reduced must find the right balance between openly disclosing a possible sub-optimal match in one vaccine component, and not discouraging vaccination uptake; vaccination may still provide benefit, especially against other viruses that may circulate in the season. Early data regarding vaccine effectiveness are not available when key messages need to be given regarding vaccination and antiviral use. Communications must be timely, repeated and transparent. The goal of communications is that public should understand that the flu vaccine may offer only partial, reduced protection, but that vaccination can continue to offer protection from illness and hospitalizations. At the same time, greater emphasis is placed on including antiviral medications as a "second line of defense" (to be used in concert with vaccination) and the importance of everyday preventive actions like covering coughs and frequent hand washing.

6. **Since the hearing another study on the high-dose influenza vaccine was published in The Lancet Infectious Diseases. The study funded by FDA, and co-authored by Centers of Medicare and Medicaid Services (CMS) and CDC personnel, found the high-dose vaccine was 22 percent more effective than standard vaccines in older populations. This finding was similar to a previous study that showed 24 percent more effectiveness. When will CDC include the high-dose vaccine on the agenda for CDC's Advisory Committee on Immunization Practices (ACIP) meeting to see if the advisory committee would be willing to express a preference for the high-dose vaccine indicated for people 65 years of age and older?**

   Answer: The Advisory Committee on Immunization Practices (ACIP) has recommended high-dose inactivated vaccine (Fluzone HD, Sanofi Pasteur) since its

licensure by the Food and Drug Administration (FDA) in 2009, and included the vaccine in the 2010-11 recommendations for use in persons ≥65 years-old. Adopting ACIP's recommendation, the Centers for Disease Control and Prevention (CDC) has included Fluzone HD , along with other flu vaccines, in the U.S. influenza vaccine recommendations each season since its approval.

ACIP is reviewing the evidence for Fluzone HD and could consider preferential language. Note that ACIP recommendations already state that Fluzone HD has been found to be more effective than standard dose vaccine in one study. More information available here: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm and http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5916a2.htm.

7. **In a future influenza season with a drifted strain and/or vaccine mismatch like this season, will the CDC defer until after the influenza season starts from issuing a health advisory that aims to raise more awareness among doctors and patients about antiviral drugs and recommends the use of these drugs as soon as possible for high risk groups? Or will CDC issue such a health advisory as soon as there is a new WHO recommendation, even if it is several weeks before the start of the U.S. influenza season?**

Answer: CDC believes that broad public communications about influenza should be data-driven and include actionable information. Consumer research indicates that the public and physicians are widely aware of the fact that how well the flu vaccine works can vary. Premature communications suggesting possible vaccine failures could have unintended public health consequences including decreased vaccine uptake which could result in greater morbidity and mortality. Needless additional unintended economic and industry consequences could result from premature communications about reduced vaccine effectiveness.

CDC believes that influenza communications this season were appropriate in their timing. Information about the appearance of drifted viruses was made public regularly. Information about the changing Southern Hemisphere vaccine formulation also was made available. CDC continues to recommend vaccination during drifted seasons for a number of reasons, including:

- We cannot know which viruses will circulate over the season. The influenza vaccine protects against three or four different influenza viruses, depending on which vaccine is administered (trivalent or quadrivalent). Vaccination can thus protect against circulating "vaccine-like" viruses. Sufficient data on which strains are actually circulating during a given season after it begins are needed to know if the predominating strains are a poor match to the vaccine.

- Antigenic characterization data is not the same as vaccine effectiveness. In the past, substantial vaccine effectiveness has been measured during drifted seasons. Antibodies created through vaccination with one influenza virus can

sometimes offer protection against drifted influenza viruses (this is called cross-protection). Thus, flu vaccination may still reduce flu illnesses, doctors' visits, and missed work and school due to flu, as well as prevent flu-related hospitalizations and deaths.

As long as vaccine may provide benefit, CDC will recommend that vaccination efforts continue and communication efforts to promote vaccination will continue. It is important to note that CDC also regularly communicates about the fact that how well the influenza vaccine works is variable.

Additionally, communicating about antiviral drugs is a core component of CDC's annual messaging and guidance. Research suggests that antiviral drugs are underutilized, thus the agency places heavy emphasis on these communication efforts routinely. Core efforts are reinforced and expanded during seasons when drifted viruses are predominating and vaccine effectiveness may be reduced. Decisions to expand communications efforts have human resource implications thus these decisions are data-driven and are made after the data supports additional intervention is warranted.

8. **What actions is CDC taking to assess the use of adjuvants to boost the effectiveness of seasonal influenza vaccine that is viewed as having substantially lower than typical effectiveness rate for a seasonal influenza vaccine? What does the current data show, and what additional data (if any) would CDC need to make such an assessment?**

Answer: DC does not have a lead role in assessing the use of adjuvants in boosting effectiveness of influenza vaccine – BARDA does have a number of activities taking place in this area. BARDA has improved influenza vaccine effectiveness by supporting the advanced development of antigen-sparing vaccines using new adjuvants for pandemic influenza vaccines towards FDA licensure. Some studies have shown that these adjuvants can provide a 6-24 fold antigen-sparing effect and greater immunogenicity for H1N1, H5N1 and H7N9 candidate vaccines, wide cross-reactivity among influenza virus A subtypes, longer duration of immunity, and priming effect for stronger booster vaccinations, Other studies in infants and elderly populations with H1N1 vaccines formulated with these adjuvants showed a greater immune response for these adjuvanted vaccines than their antigen-alone vaccine counterparts in clinical trials. Since 1997 millions of young children and elderly persons in 35 countries including Canada and many in Europe have received Novartis' Fluad®, an inactivated seasonal trivalent influenza vaccine formulated with MF-59 adjuvant, resulting in responses to many circulating seasonal influenza viruses as compared to non-adjuvanted seasonal influenza vaccine counterparts in these populations. In 2013, FDA licensed GlaxoSmithKline's adjuvanted Q-PAN H5N1 pandemic influenza vaccine.

9. Are vaccination rates the best performance metric for evaluation of CDC's performance related to influenza? Are there other performance metrics that could be used to evaluate CDC's performance?

Answer: CDC measures performance related to influenza through several metrics, of which vaccination rates are only one. Vaccination coverage rates are one important metric for performance related to influenza. There are four Healthy People 2020 targets for influenza vaccination coverage reported annually by age (children 6 months through 17 years, adults 18 years and older) and special populations (health care workers, pregnant women). Most recently, CDC has also reported interim coverage rates; these are preliminary estimates through November, which provide a useful tool to focus attention to the importance of vaccination during December and beyond and to help target attention to those groups that appear to be lagging in coverage. Following each influenza season, CDC reports final influenza coverage rates for the August through May period. Seasonal influenza vaccination coverage rates have improved over the past several years, although they are still below the Healthy People 2020 targets.

In addition to reporting vaccination coverage rates, CDC also estimates the burden of disease averted by influenza vaccination. Using a model CDC published in 2013 to estimate the number of influenza-associated illnesses and hospitalizations averted by influenza vaccination during the 2005-2013 influenza seasons, CDC provides updated estimates for each influenza season. While this estimate is a result of CDC's program, it could be a considered to be metric of the healthcare and influenza control system as a whole. In the December 12, 2014, Morbidity and Mortality Weekly Report (MMWR), CDC reported that during the 2013-2014 flu season, flu vaccination prevented an estimated 7.2 million influenza-associated illnesses, 3.1 million medically-attended illnesses, and 90,000 hospitalizations. Influenza vaccination during the 2013-2014 season thus resulted in an estimated 17% fewer adverse health outcomes associated with influenza. These outcomes are a result of the circulating strain and its severity, the influenza vaccine production, distribution and delivery system, healthcare prevention practices, and consumer behavior. These also reflect the effectiveness of currently available vaccines that season.

There are additional performance metrics that are important in assessing CDC performance related to influenza. CDC is the focal point for the gathering and analysis of data – both virologic and epidemiologic – to guide recommendations for vaccine composition and the formation of clinical guidelines for prevention and treatment of influenza. As a WHO Collaborating Center for Influenza Surveillance, the Agency serves as the lead for gathering virologic data year-round. CDC also plays an important role in the development and qualification of candidate vaccine viruses for use in the manufacture of influenza vaccines. The more global surveillance data that CDC is able to gather and analyze, the faster and more

effectively it can use these data to inform influenza vaccine development. CDC also builds capacity around the globe for other nations to create and sustain their own influenza surveillance systems. This in turn provides additional viruses or genetic information available for global surveillance.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the Assistant Secretary for
Preparedness & Response
Washington, D.C. 20201

April 13, 2015

Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Chairman Upton:

As requested in the March 9th letter from your Subcommittee on Oversight and Investigations, enclosed are the responses to the six (6) questions for me in my capacity as the Director of the Biomedical Advanced Research and Development Authority (BARDA).

Do not hesitate to let me know if you have any additional questions.

Respectfully,

[redacted]

Robin Robinson
BARDA Director
Deputy Assistant Secretary for Preparedness and Response

Dr. Robinson Questions for the Record
House Committee on Energy and Commerce Subcommittee on Oversight and Investigations
February 3, 2015

1. **How is BARDA's work improving the effectiveness of influenza vaccines?**

Answer: The Biomedical Advanced Research and Development Authority (BARDA) has supported, primarily for pandemic preparedness and response purposes, the development of more effective influenza vaccines, which have added by-product benefits for seasonal influenza. BARDA has improved the effectiveness of influenza vaccines by modernizing influenza vaccine manufacturing. This has been done through support for advanced development of cell- and recombinant-based seasonal and pandemic influenza vaccine candidates towards Food and Drug Administration (FDA) licensure and by building greater domestic vaccine manufacturing capacity. These investments have led to FDA licensure of two, first-in-class, seasonal influenza vaccines in the U.S. This includes Novartis' Flucelvax®, cell-based vaccine, in 2012 and Protein Sciences' FluBlŐk®, recombinant-based vaccine, in 2013. The underlying technologies supporting these modernized vaccines have the potential to make influenza vaccines available sooner.

BARDA has also improved influenza vaccine effectiveness by supporting the advanced development of antigen-sparing vaccines towards FDA licensure using new adjuvants for pandemic influenza vaccines. Some studies have shown that these adjuvants can provide a 6-24 fold antigen-sparing effect and greater immunogenicity for H5N1 and H7N9 vaccines. In addition, adjuvanted vaccines induced an immune response that had broader cross-reactivity within the influenza virus A subtypes, suggesting that they may provide broader protection. Clinical trial studies for infants and elderly populations who received H1N1 vaccines with these adjuvants showed a greater immune response to the adjuvanted vaccines than their antigen-alone vaccine counterparts. FDA licensed GlaxoSmithKline's Q-PAN H5N1 pandemic influenza vaccine in 2013.

BARDA, along with the National Institute of Allergy and Infectious Diseases (NIAID) and industry and academic partners, has supported the development of novel types of influenza vaccine candidates (e.g., chimeric HA stem vaccine) for seasonal and pandemic influenza. Early pre-clinical studies suggest that these candidates have potential as possible universal influenza vaccines. BARDA led the development and manufacturing of the chimeric HA stem vaccine candidates in 2014, while NIAID will conduct more clinical trials with these vaccine candidates. Additionally, BARDA launched its "More Effective –Universal Influenza Vaccines" initiative on March 16, 2015 by issuing a

Request for Proposals (RFP). More specifically, the RFP will solicit proposals for the advanced development of more effective influenza vaccine candidates.

2. **How is BARDA's work improving strain selection decisions?**

Answer: Since 2010, BARDA and the Centers for Disease Control and Prevention (CDC) have developed and utilized a vaccine strain selection process designated as the Influenza Risk Assessment Tool (IRAT). IRAT identifies novel circulating strains of influenza viruses with pandemic potential (e.g., avian H5N1, avian H7N9, swine H3N2v) based on virus pathogenicity and transmissibility. Each year, IRAT informs decision-makers regarding what vaccines should be in the national pre-pandemic influenza vaccine stockpile that BARDA manages. BARDA utilized the IRAT in 2013 to develop, manufacture, test, and stockpile H7N9 vaccines in record time.

In pilot projects with academic investigators, BARDA is supporting, through NIAID contracts and solicitations, the development of influenza vaccine strain selection using new evolutionary biology and antigen cartography technologies for both seasonal and pandemic influenza vaccines. The antigen cartography work was also supported by NIH and NIAID funding.

3. **How is BARDA's work improving influenza vaccine manufacturing, accelerating the production process, accelerating the production process, and increasing the manufacturing capacity?**

BARDA has supported the development of 18 influenza medical countermeasures since 2007. These countermeasures were used during the 2009 H1N1 pandemic and have been stockpiled for avian influenza H5N1 and H7N9 outbreaks. Since December 2005, the Department of Health and Human Services (HHS) has been supporting fundamental medical countermeasures for seasonal and pandemic preparedness activities. Following the release of the Department's *Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Review* (2010) and the President's Council of Advisors on Science and Technology (PCAST) report (2010), HHS made a mid-course adjustment and took steps to efficiently execute the pandemic influenza preparedness priorities enumerated in the review and report. For influenza vaccines, HHS set a goal of "more and better influenza vaccines sooner" meaning that we need more effective vaccines available at a faster rate and in larger quantities for both seasonal and pandemic influenza.

BARDA is directly responsible for working with industry and federal partners to: (i) support advanced development of new influenza vaccines, antiviral drugs, and diagnostic devices leading to FDA approval for the U.S. market; (ii) improve influenza vaccine

manufacturing resulting in greater vaccine production yields and availability sooner; (iii) build and maintain stockpiles of pre-pandemic influenza vaccines for the critical workforce and antiviral drugs at the federal and State levels; and (iv) expand domestic and global pandemic influenza vaccine manufacturing infrastructure and capacity multifold.

HHS has made significant progress improving vaccines and manufacturing technologies. Specifically, BARDA has partnered with industry to achieve the following:

- Modernized influenza vaccine manufacturing systems through the development and licensure of new cell- and recombinant-based influenza vaccines, as well as antigen-sparing vaccines including:

    - Flucelvax® (licensed 2012), the first cell-based seasonal influenza vaccine in the U.S.
    - FluBlØk® (licensed 2013), the first recombinant-based seasonal influenza vaccine in the U.S., and
    - Q-Pan H5N1 vaccine (licensed 2013), the first adjuvanted pandemic influenza vaccine in the U.S.

- Launched the Influenza Vaccine Manufacturing Improvement (IVMI) initiative with the National Institutes of Health (NIH), CDC, and FDA, as recommended by the PCAST. This was done to optimize a generation of high yielding vaccine seed strains and develop alternative potency and sterility assays to expedite influenza vaccine availability. The IVMI initiative improvements cut significant time off the vaccine manufacturing process and increased production yields as seen in the vaccine response to the H7N9 virus outbreaks in China in 2013. Vaccine manufacturers are testing these improvements in beta tests with H5N1, H1N1, and other influenza vaccine strains to determine their feasibility and applicability for commercial manufacturing.

- Established and maintained pre-pandemic influenza vaccine stockpiles for H5N1 and H7N9 viruses that have pandemic potential in order to immunize the critical workforce and other high risk populations rapidly at the onset of an influenza pandemic. Together, BARDA and CDC developed and implemented the Influenza Risk Assessment Tool (IRAT) in 2010 to inform the composition and prioritization of vaccines in this stockpile.

- Provided multi-fold expansion of domestic influenza vaccine production for pandemic preparedness by retrofitting older manufacturing plants (2007-2011) and

building new manufacturing facilities (2009-2012) through BARDA's public-private partnerships with industry. Today, the U.S. vaccine manufacturing capacity for pandemic influenza vaccines is ~ 500 million doses within six (6) months of pandemic onset.

- Established a national medical countermeasure (MCM) response infrastructure to develop, manufacture, and rapidly test new influenza vaccines and medical countermeasures for emerging infectious diseases, such as Ebola. This infrastructure responded in 2013 with the development, production, testing, and stockpiling of H7N9 influenza vaccines and more recently Ebola vaccine and monoclonal antibody therapeutic candidates in 2014-2015. BARDA's national response infrastructure is comprised of the following programs:
    - Nonclinical Studies Network (2011) comprises of 17 laboratories able to perform animal testing;
    - Centers for Innovation in Advanced Development and Manufacturing (CIADM) (2012) comprised of three (3) government-industrial-academic consortia to develop and manufacture MCMs for chemical, biological, radiological, and nuclear (CBRN) threats routinely and during emergencies for pandemic influenza and emerging infectious diseases such as Ebola;
    - Fill Finish Manufacturing Network (FFMN) (2013) comprised of four (4) Contract Manufacturing Organizations to provide aseptic filling of medical countermeasures for CBRN threats, pandemic influenza, emerging infectious diseases, and possibly U.S. drug shortages (pilot program between FDA and BARDA);
    - Clinical Studies Network (2014) comprised of five (5) Clinical Research Organizations to provide clinical evaluation of medical countermeasures, as needed, for man-made and natural threats including Ebola.

  The CIADMs and FFMN fulfilled the PCAST Report recommendation to expand and improve vaccine manufacturing capacity. This was done to meet the national goal of making the first dose of pandemic influenza vaccine available within 12 weeks of pandemic onset and to ensure that sufficient quantities are available to meet national demand in less than six (6) months.

- Established a global vaccine manufacturing infrastructure with the World Health Organization (WHO) in 2006 in eleven (11) developing countries to make pandemic influenza vaccines and vaccines for other diseases. This has resulted in the licensure by these partner countries of four licensed influenza vaccines and a current capacity to produce more than 300 million doses of pandemic influenza vaccine.

The HHS response to the H7N9 avian influenza outbreaks was exemplified by federal agency cooperation and public-private partnerships with industry. This was made possible by building upon lessons learned from the 2009 H1N1 pandemic and investments made in pandemic vaccine strain selection, innovations in vaccine strain development, vaccine manufacturing modernization, IVMI improvements in the vaccine manufacturing process, and the usage of new adjuvants. The HHS interagency IRAT process determined that the risk from H7N9 was significant and that it would be prudent to stockpile vaccine. BARDA played a key role in these HHS efforts including utilization of new cell- and recombinant-based flu vaccines developed with BARDA support. Secondly, to provide vaccines faster, H7N9 vaccine seeds using biosynthetic methods were developed by Novartis with BARDA support as a result of the technology derived from the HHS IVMI initiative. Finally, the Novartis CIADM in Holly Springs, North Carolina played a major role in the development, manufacturing, clinical testing, and stockpiling of H7N9 vaccines in record time.

4. **How is BARDA's work helping to improve overall recognition of influenza virus mutations?**

Since 2010, BARDA and CDC have developed and utilized IRAT to identify novel circulating strains of influenza viruses with pandemic potential (e.g., avian H5N1, avian H7N9, swine H3N2v) based on virus pathogenicity and transmissibility. IRAT informs decision-makers each year on what vaccines are needed in the national, pre-pandemic influenza vaccine stockpile that BARDA manages. BARDA utilized the IRAT in 2013 to develop, manufacture, test, and stockpile H7N9 vaccines in record time. Mutations in the viral genomes of these viruses with pandemic potential are tracked by CDC, NIH, and BARDA, as well as WHO influenza collaborating laboratories. This is done to determine whether they affect virus pathogenicity, transmissibility from animals to humans, and in some cases immunogenicity and whether they impact the viral neuraminidase gene to cause antiviral drug resistance.

BARDA is supporting the development of influenza vaccine strain selection using new evolutionary biology and antigen cartography technologies for both seasonal and pandemic influenza vaccines in pilot projects. These techniques are used to identify natural influenza virus mutations, through experimental selection, using pooled human sera from different influenza seasons. This is done to determine if these mutations confer properties to virus mutants that out compete other circulating influenza virus strains.

5. **Has BARDA's work identified any areas that could improve the speed and/or accuracy of the decision-making process for the U.S. public health response to seasonal influenza? If so, please explain.**

   In pilot projects and with academic investigators, BARDA is supporting the development of influenza vaccine strain selection using new evolutionary biology and antigen cartography technologies for both seasonal and pandemic influenza vaccines.

6. **Does any of BARDA's work relate to improving the tracking of influenza vaccine effectiveness? If so, please explain.**

   BARDA's support of pandemic influenza vaccine development includes effectiveness studies. sometimes required and regularly supported Since the licensure of GlaxoSmithKline's (GSK) Q-PAN H5N1 pandemic vaccine with AS03 adjuvant in 2013, BARDA and GSK have worked together to prepare clinical study protocols for vaccine effectiveness studies and pharmacovigilance measures to monitor adverse safety events for submission to FDA. After FDA review, BARDA and GSK will establish the necessary clinical research infrastructure for clinical investigators to conduct studies and safety registries in the event of an H5N1 pandemic. Also, these protocols and registries will serve as templates for similar clinical vaccine effectiveness and pharmacovigilance studies for other pandemic influenza vaccines.

   Additionally, BARDA has developed an interactive SAP-based computer-modeled tracking tool to determine the flow of pandemic influenza vaccine from the vaccine manufacturers to the distributors. From there, a tracking tool which interfaces with CDC's SAP-based system can monitor the flow of influenza vaccine from the distributors to the actual healthcare providers administering the vaccine. Pandemic influenza exercises are planned for 2015. These exercises will test the information flow, reliability, and limits of these coordinated tracking tool systems.

   BARDA, along with influenza vaccine manufacturers, is developing two-dimensional bar codes on vaccine vials and packaging. This is being done to ensure that more comprehensive information can be readily disseminated, collected, analyzed rapidly, and utilized to track the flow of vaccine supply from manufacturers to distributors, and to retailers and healthcare providers.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

APR 0 8 2015

Dear Mr. Chairman:

Thank you for giving the Food and Drug Administration (FDA or the Agency) the opportunity to testify at the February 3, 2015, hearing before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, entitled "Examining the U.S. Public Health Response to Seasonal Influenza." This is a response to your letter of March 9, 2015.

We have restated the questions below in bold, followed by our responses.

1. **Has FDA ever approved a monovalent influenza vaccine to target a drifted seasonal influenza strain? If so, when? What were the circumstances? What legal authorities were required for the approval?**

Influenza viruses continually undergo changes in their genetic makeup and the resulting proteins that interact with the immune system. Minor changes in the protein structure in influenza viruses, known as "antigenic drift," occur frequently, enabling the virus to cause repetitive influenza outbreaks by evading immune recognition.

In 1986, FDA approved a monovalent influenza vaccine to supplement the trivalent influenza vaccine to address a drift of the H1N1 strain. The summary minutes from the July 1986 Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting demonstrate that the meeting was not devoted to influenza, but included several agenda items, and it was during this meeting that the advisory committee received an update on outbreaks of influenza that were occurring. The outbreaks were attributed to an H1N1 strain not previously selected for inclusion in the vaccine. At the time of strain selection, there was very little information available on the H1N1 strains circulating globally, but at the time of this particular meeting, some limited laboratory and epidemiological data had become available. Taking into consideration the manufacturing timelines, the committee recommended a monovalent H1N1 vaccine, but acknowledged that it was uncertain whether such a vaccine was needed or should be produced. Approximately 7 million doses of the 1986 monovalent vaccine were manufactured and distributed late in 1986.[1]

Below is the relevant text, copied from the July 1986 VRBPAC summary minutes:

[1] CDC Morbidity and Mortality Weekly Report (MMWR() 37 (31) p. 469.

4. The committee was briefed on recent outbreaks of influenza involving H1 strains with significant antigenic variation from the H1 strain (A Chile/83) which was recommended for inclusion in the trivalent vaccine formulation for the 1986-87 influenza season. At the time that decision was made, there was very little information available on H1N1 strains circulating in the world. Very recently, outbreaks with the new H1 variant have been laboratory confirmed in Singapore, Hong Kong, Taiwan and Japan. Other outbreaks have been reported but are not yet laboratory confirmed. The limited laboratory and epidemiological data which were available were reviewed. The issue before the committee was whether an additional monovalent H1N1 vaccine based on the new variants should be produced to supplement the trivalent vaccine which has already been prepared.

The committee noted that it did not have sufficient epidemiological data - attack rates, identification of at risk target populations, severity of disease, etc. - to resolve the scientific issue of whether the H1N1 monovalent vaccine is needed or should be produced. However, it was also noted that the committee is constrained by a more pragmatic factor: the manufacturers informed the committee that they believed a delay of 3 to 4 weeks (i.e. to mid August) in making a decision about whether to produce the vaccine would mean that the vaccine could not be available until January or February, when it might be too late for effective use for the flu season. To delay making the decision until September would, in the manufacturers' judgments make it virtually impossible to have the vaccine available for any part of the upcoming influenza season. The manufacturers believe that an immediate decision is required. The committee noted that if the manufacturers are correct, waiting for adequate epidemiological data would preclude the possibility of producing the monovalent H1N1 variant vaccine for the upcoming flu season. Under these circumstances, the committee recommended that if the manufacturer's are correct in their assumptions, the 1986 H1N1 variant strains, represented by A/Taiwan/1986 should be included in a supplemental vaccine for the 1986-87 flu season.

In addition to "antigenic drift" major changes, known as "antigenic shift," can also occur and have the potential to lead to a pandemic, as the world experienced in 2009, for which a monovalent influenza vaccine was approved and utilized to respond to the influenza pandemic.

We note that vaccines are approved under section 351 of the Public Health Service Act.

2. Has there ever been a delay in the production of an influenza vaccine because a vaccine manufacturer was waiting for FDA to provide the reagents? If so, when? What were the circumstances?

To our knowledge, the United States has never experienced an untimely delay in the production or availability of influenza vaccine because a manufacturer was waiting on FDA to provide the reagents needed for manufacture.

3. **In August 2010, the President's Council of Advisors on Science and Technology (PCAST) issued a report on reengineering the influenza vaccine production enterprise. The report recommended that the FDA should develop and issue a guidance document**

that defines a clear regulatory pathway for the approval of adjuvants. What actions, if any, has FDA taken to implement this recommendation?

This question refers to PCAST recommendation 6-2: DEVELOP ADJUVANT GUIDANCE DOCUMENT:

"Adjuvants can be an important mid-term solution to vaccine supply and will be an essential component to a long-term solution of developing recombinant protein-based influenza vaccines. The FDA should develop and issue a guidance document that defines a clear regulatory pathway for the approval of adjuvants for use in human vaccines, including those for seasonal and pandemic influenza. This guidance document should define the goals for adjuvant use (i.e., dose sparing, boosting efficacy in the elderly), specify rational endpoints for clinical trials, and stipulate safety criteria. Because the safety and efficacy of adjuvants can only be evaluated in the context of the final vaccine product, the current practice of approving final products, as opposed to adjuvants alone, is a rational one."

FDA has taken the following recent actions, with respect to adjuvants:

- Worked with other national regulatory authorities (NRAs) through the World Health Organization (WHO) on a document entitled "Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines." This guideline document was published by WHO in 2013 and constitutes guidance for NRAs and for manufacturers of biological products on the nonclinical evaluation of adjuvants and adjuvanted vaccines, the type of data needed to justify the inclusion of adjuvant in the vaccine as well as considerations for early clinical trials. FDA does not plan to write a separate guidance document on adjuvanted seasonal influenza vaccines, as the WHO guidelines document on adjuvants and adjuvanted vaccines that FDA and other NRAs developed reflects an international consensus. The current FDA guidance documents on influenza vaccines also apply to adjuvanted influenza vaccines. In 2013, FDA licensed an adjuvanted H5N1 influenza vaccine, manufactured by GlaxoSmithKline Biologicals.

4. **The PCAST report also recommended that FDA should develop a well-defined regulatory process for introducing alternative assays for seasonal influenza vaccines. What action, if any, has FDA taken to implement this recommendation? Have any alternative assays for flu vaccines been approved in the last three years?**

This question refers to PCAST recommendation 3-3: POTENCY TESTING

"FDA and BARDA should fund applied research to develop rapid methods for making potency assays for testing inactivated influenza vaccines. This should be a high-priority effort carried out through a combination of in-house programs at FDA and contracts to companies, aimed at creating and implementing such methods within a 2-3 year time frame. Possible methods include mass spectroscopy coupled with molecular biological techniques for making affinity reagents. Such methods will need to be carefully validated by comparison with the standard radial immunodiffusion assay. In addition, FDA should develop a well-defined regulatory process for introducing alternative assays for HA potency for seasonal influenza vaccines, initially alongside existing assays."

FDA has taken the following recent actions, with respect to developing alternative assays:

- The Agency has been working closely with the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC) in supporting development of new, faster, and better potency assays to measure the amount of active viral hemagglutinin (HA) protein in inactivated influenza vaccine lot release samples as part of the HHS Influenza Vaccine Manufacturing Improvement (IVMI) initiative recommended by the PCAST report (2010).

- Promising alternative potency assays being developed at FDA include an Enzyme-Linked Immunosorbent assay (ELISA) and a Surface Plasmon Resonance (SPR) assay. Both of these approaches are being designed to replace the Single Radial Immunodiffusion (SRID) assay for both multivalent seasonal and monovalent pandemic vaccine potency determination and are ready for comparison studies. They are being evaluated for feasibility to accurately measure HA in influenza vaccines in comparison to the SRID assay, as well as their suitability to monitor vaccine stability.

5. The PCAST report recommended that FDA should define a regulatory process to guide development and implementation for sterility testing of influenza vaccines. Has FDA implemented this recommendation?

This question refers to PCAST recommendation 3-4: DEVELOP PLATFORM TECHNOLOGY FOR STERILITY TESTING:

"The FDA and BARDA should support the development of rapid methods to test the sterility of influenza vaccines, through such molecular biological techniques as PCR and shotgun DNA sequencing. This should be carried out through private sector contracts and in collaboration with manufacturers. The methods should be performed in parallel with existing sterility testing of seasonal influenza vaccines, to demonstrate the sensitivity and validity of the methods. The FDA should define a regulatory process to guide development and implementation."

FDA has taken the following recent actions with respect to sterility testing:

- Effective June 2012, FDA amended the sterility test requirements for biological products to acknowledge the advancement in new sterility test methods that yield accurate and reliable test results in less time. The final rule provided manufacturers of biological products greater flexibility and encouraged use of the most appropriate and state-of-the-art methods for ensuring the safety of biological products.

- FDA and BARDA are working with the vaccine manufacturers and several sterility assay companies to evaluate, optimize, and validate new rapid sterility methods as part of the IVMI initiative recommended by the PCAST report (2010). For example, one sterility method supported under this initiative by BARDA takes only five days, rather the usual 14 days, to obtain results and is under evaluation not only by influenza vaccine manufacturers but by manufacturers of other pharmaceutical products as a time- and cost-saving measure throughout their aseptic manufacturing processes. The goal is to develop a new platform for automated rapid sterility testing that will reduce the time it takes to

perform sterility testing from the current 14-day method prescribed by the U.S. Pharmacopeial Convention (USP). For example, there is published literature describing rapid sterility testing. In 2011, FDA published a paper that concluded that the Rapid Milliflex Detection System, utilizing Schaedler blood agar (SBA) medium, appears to be a promising rapid alternate method to the compendial sterility method, having the advantage of taking only five days for sterility testing of biological products, including inactivated influenza vaccines.[2]

Thank you, again, for contacting us concerning this matter. FDA will continue to work with U.S. Government partners, manufacturers, and other stakeholders to facilitate development of new vaccines and identify methods that have the potential to speed the manufacturing process for existing vaccines.

If you have additional questions, please let us know.

Sincerely,

[redacted]

Thomas A. Kraus
Associate Commissioner for Legislation

cc: The Honorable Fred Upton
Chairman
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce

[2] Parveen S, Kaur S, Wilson David SA, Kenney JL, McCormick WM, Gupta RK. Evaluation of growth-based rapid microbiological methods for sterility testing of vaccines and other biological products. *Vaccine* 2011 Oct 19; 29 (45):8012-23.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

April 2, 2015

The Honorable Tim Murphy
Chairman, Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your March 9, 2015, letter about the U.S. public health response to seasonal influenza. I am pleased to respond to your questions.

1. How is NIAID's work improving the effectiveness of influenza vaccines?

The National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute of the National Institutes of Health (NIH) for research on infectious diseases, including influenza. NIAID's long-standing influenza research program supports research to improve the effectiveness of influenza vaccines. These efforts include studies to develop new vaccine technologies, to boost the immune response to vaccines, and to develop "universal" influenza vaccine candidates that could provide lasting protection against multiple strains of influenza.

NIAID research has contributed to the development of innovative influenza vaccine technologies that have improved effectiveness of influenza vaccines for specific populations. For example, NIAID supported the first clinical trials of a high-dose influenza vaccine developed by Sanofi Pasteur and approved for use among the elderly by the U.S. Food and Drug Administration (FDA) in 2009. NIAID also supported early-stage development of Flublok, the first vaccine using recombinant influenza vaccine technology instead of the more time-intensive egg-based culture for virus growth. Flublok was approved by FDA for use in adults; because it does not contain egg proteins, Flublok provides a potential alternative to egg-based vaccines for individuals with egg allergies. Recombinant influenza vaccine technology also could facilitate rapid startup of vaccine manufacturing and may be useful in the event of a pandemic or vaccine shortage.

In addition, NIAID-supported researchers are investigating ways to enhance the immune response to current licensed seasonal influenza vaccines, including through the use of adjuvants. For example, NIAID Vaccine Research Center (VRC) researchers are conducting clinical trials on various DNA prime-boost vaccine combinations with the goal of improving the potency and durability of current licensed seasonal influenza vaccines. NIAID also funded a large clinical

trial to evaluate an intradermal influenza vaccine, approved for use by the FDA in 2012, which requires less antigen to achieve the same effectiveness as previously licensed seasonal influenza vaccines. This vaccine formulation and similar technologies could help to extend available vaccine supplies.

NIAID's Vaccine Treatment and Evaluation Units (VTEUs), part of the Institute's long-standing clinical research infrastructure, have allowed NIAID to rapidly test new influenza vaccines and vaccination strategies and to respond to emerging public health concerns, such as the 2009 H1N1 pandemic. NIAID also participates in the Influenza Vaccine Manufacturing Improvement Initiative in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), the Centers for Disease Control and Prevention (CDC), and FDA. Under this initiative, NIAID is supporting efforts to develop higher-yield influenza virus vaccine strains, improve influenza strain selection, and develop novel assays to accelerate vaccine production. NIAID research also is helping to improve the effectiveness of vaccines to protect against influenza strains with pandemic potential. NIAID intramural researchers, in collaboration with the biotechnology company MedImmune, are generating candidate live, attenuated influenza virus vaccines against such strains. These vaccines are being evaluated in preclinical and clinical studies and could be an important tool in a rapid response to emerging pandemic strains.

NIAID has intensified efforts to develop an effective universal influenza vaccine candidate capable of eliciting a broad and potent immune response against a wide range of distinct influenza viruses. NIAID is collaborating with BARDA and CDC to investigate the human immune response to universal influenza vaccines in a planned Phase I clinical trial in the VTEU network. In addition, the NIAID VRC is developing a promising universal influenza vaccine strategy based on the use of self-assembling ferritin nanoparticle technology to increase the breadth and magnitude of the immune response. A successful universal influenza vaccine could address the problem of variable vaccine efficacy by reducing or eliminating the need for yearly seasonal influenza vaccines.

2. How is NIAID's work improving strain selection decisions?

NIAID has a long-standing commitment to basic and clinical research on influenza to better understand how influenza strains emerge, evolve, and infect animals and humans. Although NIAID has no role in the selection of strains for seasonal influenza vaccines, NIAID has developed new technologies and surveillance networks to help understand the evolution of influenza virus strains and inform influenza vaccine strain selection.

NIAID is supporting cutting-edge research on influenza genomics to gather critical data about influenza viral evolution and circulating strains that will help inform strain selection. NIAID has promoted the use of next-generation sequencing through the Influenza Genome Sequencing Project (IGSP) and the Influenza Research Database (IRD). The IGSP has sequenced the complete genetic blueprint of more than 16,000 influenza viruses and made this information publicly available through databases such as IRD and GenBank at the National Center for Biotechnology Information. NIAID also has supported the development of novel

bioinformatics and data analysis platforms, such as Antigenic Cartography and Antibody Landscaping, which could one day help predict which viral strains may emerge in the future.

In addition, NIAID's Centers of Excellence for Influenza Research and Surveillance (CEIRS) Program is supporting researchers around the world to study the factors that control the emergence and transmission of influenza viruses among animal reservoirs, and the immunological determinants of whether an influenza virus causes only mild illness or results in severe disease or death. The CEIRS Program continually monitors cases of animal and human influenza worldwide to rapidly detect and characterize viruses that may have pandemic potential, such as the avian influenza strains H5N1 and H7N9. CEIRS Program research augments surveillance efforts by the CDC, the World Health Organization, and others, helping to create a more comprehensive picture of the incidence and characteristics of influenza virus strains worldwide to better inform influenza vaccine strain selection decisions.

3. How is NIAID's work helping to improve overall recognition of influenza virus mutations?

NIAID recognizes the critical need to develop a more comprehensive understanding of seasonal and pandemic influenza viruses and plays a leading role in efforts to characterize their evolution and pathogenesis. NIAID supports essential research and surveillance efforts to identify and track the appearance and spread of established and mutated influenza virus strains to shed light on the emergence, evolution, and severity of influenza pandemics as well as seasonal influenza.

The NIAID-supported Centers of Excellence for Influenza Research and Surveillance (CEIRS) Program brings together multidisciplinary teams of researchers that are collecting thousands of influenza viruses from humans and animals in the United States and throughout the world. The CEIRS investigators rapidly characterize these viruses to evaluate their pandemic potential and to determine if they have specific mutations associated with enhanced disease or resistance to antiviral drugs. In conjunction with these efforts, the NIAID intramural research program aims to map viral virulence factors that determine the occurrence and severity of infection in different animal hosts. NIAID researchers are investigating the dynamics of viral mutations associated with different hosts and characterizing the host response to infection.

NIAID-supported researchers also are investigating how influenza viruses mutate and how these mutations influence transmission and disease severity. As discussed in the response to question 2, NIAID supports the sequencing and cataloging of full influenza genomes in public databases, providing additional information to researchers about changes in the influenza virus. Taken together, these efforts provide public health officials with essential information that can be used to identify the emergence and spread of specific strains, as well as strengthen the development of public health strategies crucial to lessening the impact of seasonal influenza and responding to a potential pandemic.

Thank you for your continuing commitment to public health preparedness. I hope that this information is helpful to you. I will provide a copy of this letter to Representative Diana DeGette, the co-signer of your letter. Best personal regards.

Sincerely,

[redacted]

Anthony S. Fauci, M.D.
Director
National Institute of Allergy
and Infectious Diseases

cc: Representative Diana DeGette

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

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July 29, 2015

The Honorable Sylvia Burwell
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Burwell:

Pursuant to Rules X and XI of the U.S. House of Representatives, the Committee on Energy and Commerce is continuing its examination of the U.S. public health response to seasonal influenza. We received HHS's response to our letter dated March 9, 2015, as well as the responses from HHS agencies involved in seasonal influenza preparedness activities (National Institutes of Health, Centers for Disease Control and Prevention, Food and Drug Administration, and Biomedical Advanced Research and Development Authority). The responses are attached for your reference.

The mismatched seasonal influenza vaccine and the high death rate among the elderly and other high-risk populations in the U.S. during the 2014-2015 influenza season highlight the need for an improved response, including making seasonal influenza vaccines more effective and promptly available. We believe understanding the lessons from the 2014-2015 influenza season could improve the U.S. public health response in the future and possibly save thousands of lives. We write to seek further information on HHS's current preparedness efforts for the 2015-2016 influenza season, and to work with you to improve the nation's response to seasonal influenza.

To assist the committee, please provide the following by August 12, 2015:

Unredacted versions of any documents sent to and/or from you or the Office of the Secretary that discuss recommendations or lessons learned from the 2014-2015 influenza season or preparations for the 2015-2016 influenza season, and/or any unredacted versions of documents related to a briefing or briefings for you or the Office of the Secretary in 2015 on seasonal influenza vaccine mismatch issues.

Production of the documents will facilitate our investigation and an accurate understanding of the facts. The committee seeks to work cooperatively with HHS to safeguard any sensitive information to address any concerns in this area.

Please also respond by August 12, 2015 to the following questions:

1. What are the mismatch risks this year? What are the contingency plans for the upcoming 2015-2016 season in the event of a mismatch?

2. CDC has provided a 94 percent expected coverage estimate for the mammalian cell propagated parent of the egg-adapted H3N2 strain, which appears to have undergone significant antigenic change during egg passage. What is the expected coverage by the egg-adapted H3N2 strain in most of the vaccine supply for the 2015-16 influenza season?

3. Seasonal influenza has significant health and economic impacts, and in some cases greater impact than in a pandemic. For example, the 2009 H1N1 pandemic resulted in about 12,000 deaths, but close to 50,000 deaths have resulted from seasonal influenza when the H3N2 strain is dominant such as in the most recent influenza season. According to the World Health Organization (WHO), annual seasonal influenza epidemics result in about 3 million to 5 million cases of severe illness and about 250,000 to 500,000 deaths worldwide, which is likely an underestimation. As noted in a 2012 report by the Center for Infectious Disease Research & Policy, "[T]hese figures indicate that the cumulative health impact of seasonal influenza over the last century rivals the potentially explosive, but time-limited, impact of the four pandemics of the past 100 years."

   Given that the health and economic impacts of severe influenza outbreaks are significant, and arguably on par with other threats such as Ebola, MERS, H5N1 and H1N1 for which public health emergency declarations and Public Readiness and Emergency Preparedness (PREP) Act declarations have been used to support availability of medical counter-measures, should seasonal influenza outbreaks (for example, in the event of a vaccine mismatch) be considered public health emergencies?

4. According to the FDA response, a monovalent rescue vaccine was prepared in response to a possible vaccine mismatch because of a drifted (H1N1) strain for the 1986-1987 season in July 1986, even though there was very little information about the mismatch. In contrast, no action was taken in the early summer of 2014 for emerging evidence of a drifted strain in the 2014-2015 season, even though CDC testified that the mismatch was around 36 percent at the time. The CDC witness testified at the February 3 oversight hearing that by the time a 50 percent mismatch was determined in September 2014, it was too late to pursue a monovalent vaccine. However, CDC's acting influenza division director told committee staff in a briefing by telephone that a mismatch between 20-30 percent would be significant evidence of drift.

   (a) What criteria will trigger action on pursuing a monovalent rescue vaccine in the event of a mismatch?

(b) Under what circumstances would it be appropriate to pursue a monovalent rescue vaccine to respond to a drifted seasonal influenza strain?
(c) Are there any contingency plans for a monovalent rescue vaccine in the event of a seasonal influenza vaccine mismatch?

5. A recent CDC study that examined clinician treatment practices for outpatients with influenza during the 2012-2013 season showed that only 16 percent of patients with laboratory-confirmed influenza were prescribed antiviral drugs, while as many as 30 percent were prescribed one of three common antibiotics. In light of such findings, should there be greater emphasis and timeliness in federal public communications about the use of antiviral medications as a "second line of defense" against seasonal influenza?

6. According to the HHS website, flu.gov, 90 percent of influenza-related deaths and more than half of influenza-related hospitalizations occur in people age 65 and older. Last year's severe influenza season was reportedly the deadliest for seniors in five years. A recent study showed that a new high-dose vaccine was 24.2 percent more effective in preventing influenza in adults 65 years and older relative to a standard-dose vaccine. Another study based on data from more than 2 million Medicare beneficiaries suggests that the high-dose influenza vaccine works better than a standard-dose vaccine for preventing probable influenza illness and influenza-related hospital admissions in elderly people. The study, published by the journal *The Lancet Infectious Diseases*, was funded by the FDA and included authors from that agency as well as from the Center for Medicare and Medicaid Services and the CDC. The CDC says it has not expressed a preference for either the high-dose or standard vaccine, but that the new findings will be considered in the future policy deliberations of the CDC's Advisory Committee on Immunization Practices (ACIP). CDC told committee staff in a briefing that the high-dose vaccine would not be on the CDC's ACIP agenda until February 2016. In light of these studies, is there any way to expedite consideration of these studies to see if CDC should express a preference on high-dose vaccines?

7. The Department's response stated that HHS/CDC purchases and distributes approximately 10 to 15 percent of the total seasonal influenza vaccines available in the United States each year through CDC's Vaccines for Children and Section 317 Immunization Programs. What are the total annual expenditures for seasonal influenza vaccines under these programs? Does HHS/CDC use its purchasing power to require measurement of outcomes for the seasonal influenza vaccines it purchases (i.e., vaccine effectiveness as measured by the degree of match of the vaccine to circulating seasonal strains or reductions in deaths or hospitalizations)? If so, what are the measurements, and what have they shown?

8. Has there ever been an emergency use authorization and/or an expanded use authority to allow use of an unlicensed seasonal influenza vaccine?

An attachment to this letter provides additional information about how to respond to the committee's request. If you have any questions regarding this request, please contact Alan

Slobodin with the majority committee staff at (202) 225-2927 and Una Lee with the minority committee staff at (202) 225-3641.

Sincerely,

Fred Upton
Chairman

Frank Pallone, Jr.
Ranking Member

Tim Murphy
Chairman
Subcommittee on Oversight
and Investigations

Diana DeGette
Ranking Member
Subcommittee on Oversight
and Investigations

Attachments: Instructions on Responding to Committee Document Requests

April 27, 2015 letter from HHS Assistant Secretary for Legislation Jim R. Esquea

April 13, 2015 letter from BARDA Director Robin Robinson

April 9, 2015 letter from CDC Director Thomas R. Frieden

April 8, 2015 letter from FDA Associate Commissioner for Legislation Thomas A. Kraus

April 2, 2015 letter from NIAID Director Anthony S. Fauci

cc: Dr. Thomas Frieden, Director, CDC

Dr. Stephen Ostroff, Acting Commissioner, FDA

Dr. Robin Robinson, Director, BARDA

Dr. Anthony Fauci, Director, National Institute of Allergies and Infectious Diseases.

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

September 30, 2015

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Thank you for your July 29, 2015, letter regarding the public health response to seasonal influenza. Enclosed are responses to the questions you posed in your letter.

I hope this information is helpful to you. Thank you for your continued commitment to public health preparedness.

Sincerely,

[redacted]

Jim R. Esquea
Assistant Secretary for Legislation

cc: The Honorable Frank Pallone, Jr.
Ranking Member

Enclosure

Enclosure

1. **What are the mismatch risks this year? What are the contingency plans for the upcoming 2015-2016 season in the event of a mismatch?**

   In June 2015, the Centers for Disease Control and Prevention (CDC) reported to the Committee via email that "through late May, more than 90% of the U.S. influenza viruses tested by CDC were characterized as being antigenically 'like' or 'similar to' the vaccine viruses recommended for the 2015-2016 Northern Hemisphere influenza vaccine. These proportions remain similar to those reported in late February/early March at the WHO [World Health Organization] Vaccine Consultation Meeting and the FDA's [Food and Drug Administration] Vaccines and Related Biological Products Advisory Committee."

   The proportion of U.S. viruses collected since October 2014 that are antigenically similar to vaccine viruses recommended for the Northern Hemisphere influenza vaccine has remained constant and remains above 90 percent (93.7 percent as of July 30, 2015). This indicates U.S. A(H3N2) viruses from spring and early summer were antigenically similar to the 2015-2016 A(H3N2) vaccine virus. Influenza viruses, however, are notoriously unpredictable as they constantly undergo some degree of genetic change. These changes can be small and may accumulate over time (antigenic drift) or may be rapid and lead to a pandemic (antigenic shift). CDC cannot predict the exact timing, geography or severity of an upcoming influenza season, which types/subtypes of influenza viruses will predominate in a given year, or whether circulating viruses will undergo changes before or during a season that may result in antigenic differences between circulating and vaccine viruses. For these reasons, it is not possible to provide a "risk of mismatch" assessment for the season before it has begun.

   Contingency plans in the event of the circulation of a virus that has undergone significant antigenic drift during the 2015-2016 influenza season include both those from previous years as well as new efforts. More frequent and comprehensive communication with Department of Health and Human Services (HHS) leadership and FDA has been implemented, and FDA has done likewise with the Chair of its Vaccines and Related Biological Products Advisory Committee regarding influenza virus surveillance data, including any evidence for viral antigenic drift and potential seasonal influenza vaccine.

   In general, there are HHS-wide plans for a variety of influenza scenarios. CDC's contingency plan in the event that a drifted strain emerges late, after the vaccine production and distribution process has begun, is to emphasize the use of other tools and strategies in the arsenal to fight the flu. As during the 2014-2015 influenza season, CDC emphasizes the use of antiviral medications as a "second line of defense," promotes pneumococcal vaccination for seniors to help mitigate the complications of flu in the elderly, and stresses the importance of everyday preventive actions like covering coughs, social distancing, and frequent hand washing. CDC would expect to implement this same evidence-based approach if faced with a similar flu season in the future. During a "drift" season, CDC would continue to recommend influenza vaccination because the vaccine will likely still offer some protection, and it is likely that other influenza subtypes that the vaccine is well matched to will continue to circulate. For example, during the 2014-2015 influenza season (when the H3N2 component of the vaccine was antigenically different from

most circulating H3N2 viruses) there was a late season predominance of influenza B viruses, which were antigenically similar to viruses in the seasonal vaccine. CDC is working to strengthen antiviral treatment practices since these are not yet well implemented but can be of greater importance during years with substantial drift.

2. **CDC has provided a 94 percent expected coverage estimate for the mammalian cell propagated parent of the egg-adapted H3N2 strain, which appears to have undergone significant antigenic change during egg passage. What is the expected coverage by the egg-adapted H3N2 strain in most of the vaccine supply for the 2015-16 influenza season?**

We assume that the question above relates to vaccine effectiveness. It is important to understand that there is a difference between antigenic match and vaccine effectiveness. As CDC reported to the Committee in writing in April, at least two factors play an important role in determining the likelihood that flu vaccine will protect a person from flu illness: the characteristics of the person being vaccinated (such as their age and health) and the similarity or "match" between the flu viruses contained in the vaccine and the flu viruses spreading in the community. CDC determines if circulating viruses are well-matched to the reference virus used to derive the vaccine virus through antigenic characterization using biological tests and genetic characterization.

The relationship between vaccine match, as determined by these laboratory methods, and vaccine effectiveness is not straightforward. Even when we identify a drifted strain via the methods above, we cannot predict how well the vaccine will work until the proper epidemiologic field studies are conducted once the influenza season has begun. We have accelerated the pace of these studies over the last several years so that we get interim results as quickly as possible during the season, but final estimates of how effective a vaccine actually was in people are not available until after the season is over.

CDC did not provide "coverage" estimates for the 2015-2016 season. As of July 30, 2015, the majority of U.S. viruses collected and tested since October 1, 2014, were antigenically similar to the respective influenza A and B vaccine viruses recommended for the 2015-16 Northern Hemisphere influenza vaccine, including 93.7 percent of the H3N2 viruses antigenically characterized during this period. CDC reports regularly during the year, and weekly during the influenza season, on the properties of the hemagglutinin protein of circulating influenza viruses and the level of antigenic similarity to reference viruses that are identified as suitable viruses from which to derive vaccine virus candidates. Seasonal influenza viruses are propagated primarily in mammalian cells as routine propagation in eggs is difficult and may introduce genetic changes that can alter the antigenic characteristics of the virus. Therefore, antigenic similarity for influenza A(H3N2) viruses is determined based on similarity with a reference virus also grown in mammalian cells. The antigenic similarity to A/Switzerland/9715293/2013 virus, the recommended A(H3N2) component for the 2015-16 Northern Hemisphere vaccine, is based on the virus propagated in mammalian cells. This provides the most accurate characterization of viruses circulating in humans.

The majority of influenza vaccines manufactured in the United States are grown in embryonated chicken eggs. As human influenza viruses adapt for high growth in eggs, which is typically

needed to produce enough antigen for large scale vaccine production, genetic changes can occur in the viruses. These are called "egg-adapted" changes. Some egg-adapted changes may have antigenic (or immunogenic) implications while others may not.

When characterizing influenza viruses as potential vaccine viruses, it is usual to compare the egg-propagated virus with its mammalian cell-propagated counterpart to ensure that the egg-adaptation has not introduced undesirable antigenic changes. The A/Switzerland/9715293/2013 virus used for the 2015-2016 season was evaluated in this way. While there are some egg-adaptations in the A/Switzerland/9715293/2013 vaccine viruses, WHO selected this virus as a candidate vaccine virus because it had egg adaptations that had the least impact compared to other candidates, and was antigenically similar to the majority of circulating viruses. Other egg-propagated viruses were also evaluated, but were found to be unsuitable.

3. **Seasonal influenza has significant health and economic impacts, and in some cases greater impact than in a pandemic. For example, the 2009 H1N1 pandemic resulted in about 12,000 deaths, but close to 50,000 deaths have resulted from seasonal influenza when the H3N2 strain is dominant such as in the most recent influenza season. According to the World Health Organization (WHO), annual seasonal influenza epidemics resulted in about 3 million to 5 million cases of severe illness and about 250,000 to 500,000 deaths worldwide, which is likely an underestimation. As noted in a 2012 report by the Center for Infectious Diseases Research & Policy, "[T]hese figures indicate that the cumulative health impact of seasonal influenza over the last century rivals the potentially explosive, but time-limited, impact of the four pandemics of the past 100 years."**

   Given that the health and economic impacts of severe influenza outbreaks are significant, and arguably on par with other threats such as Ebola, MERS, H5N1 and H1N1 for which public health emergency declarations and Public Readiness and Emergency Preparedness (PREP) Act declarations have been used to support availability of medical countermeasures, should seasonal influenza outbreaks (for example, in the event of a vaccine mismatch) be considered public health emergencies?

   The Secretary of HHS has discretionary authority to declare a public health emergency, issue a declaration under the PREP Act, or make other determinations regarding a public health emergency as warranted by the circumstances.

   The Secretary may, under section 319 of the Public Health Service (PHS) Act determine, after consultation with such public health officials as may be necessary, that a) a disease or disorder presents a public health emergency; or b) that a public health emergency, including significant outbreaks of infectious disease or bioterrorist attacks, otherwise exists. Several legal authorities flow from a public health emergency declaration. For example, if the President has also declared an emergency or major disaster under the Stafford Act or National Emergencies Act, the Secretary may authorize the Centers for Medicare & Medicaid Services to waive certain conditions of participation or sanctions in accordance with section 1135 of the Social Security Act. However, many of the authorities the Secretary may employ during a response to a pandemic or infectious disease outbreak do not require a declaration of a public health emergency. For example, without declaring a public health emergency, the Secretary may

conduct research and clinical trials of countermeasures, deploy countermeasures from the Strategic National Stockpile, provide temporary assistance to States and localities, take actions to control the spread of communicable disease, and deploy the National Disaster Medical System. For more information on public health emergency declarations, please see http://www.phe.gov/Preparedness/support/secauthority/Pages/default.aspx and http://www.phe.gov/Preparedness/legal/Pages/phedeclaration.aspx.

The PREP Act authorizes the Secretary of HHS to issue a declaration that provides immunity from liability (except for willful misconduct) for claims of loss caused, arising out of, relating to, or resulting from administration or use of countermeasures to diseases, threats and conditions determined by the Secretary to constitute a present, or credible risk of a future public health emergency to entities and individuals involved in the development, manufacture, testing, distribution, administration, and use of such countermeasures. A PREP Act declaration is specifically for the purpose of providing immunity from liability, and is different from, and not dependent on, other emergency declarations. While the PREP Act states that a covered countermeasure must be a 'qualified pandemic or epidemic product' or 'security countermeasures,' current pandemic influenza PREP Act declarations provide liability immunity for countermeasures against pandemic influenza A viruses and influenza A viruses with pandemic potential. The current PREP Act declaration for pandemic influenza also specifies that liability immunity is available under the Act and the declaration for pandemic influenza vaccines until they are covered under the Department's National Vaccine Injury Compensation Program (VICP). The VICP provides a separate liability protection mechanism for vaccines that are recommended for use in children and for which Congress has passed an excise tax. Seasonal influenza vaccines generally are covered by the VCIP. For more information on the PREP Act, please see http://www.phe.gov/Preparedness/legal/prepact/Pages/prepqa.aspx. For more information on the VCIP, please see http://www.hrsa.gov/vaccinecompensation/index.html.

The Secretary may also determine under section 564 of the Federal Food, Drug, and Cosmetic Act that there is a public health emergency or a significant potential for a public health emergency that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a biological, chemical, radiological or nuclear agent(s), or a disease or condition that may be attributable to such agent(s). She may then determine that the circumstances justify emergency authorization of unapproved products or unapproved uses of approved products, permitting FDA to issue Emergency Use Authorizations for such products. For more information about Emergency Use Authorizations, please see http://www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/mcmlegalregulatoryandpolicyframework/ucm182568.htm.

4. **According to the FDA response, a monovalent rescue vaccine was prepared in response to a possible vaccine mismatch because of a drifted (H1N1) strain for the 1986-1987 season in July 1986, even though there was very little information about the mismatch. In contrast, no action was taken in the early summer of 2014 for emerging evidence of a drifted strain in the 2014-2015 season, even though CDC testified that the mismatch was around 36 percent at that time. The CDC witness testified at the February 3 oversight hearing that by the time a 50 percent mismatch was determined in September 2014, it was too late to**

pursue a monovalent vaccine. However, CDC's acting influenza division director told committee staff in a briefing by telephone that a mismatch between 20-30 percent would be significant evidence of drift.

(a) What criteria will trigger action on pursuing a monovalent vaccine in the event of a mismatch?

The decision to produce an off-cycle monovalent seasonal influenza vaccine is not made based solely upon the percentages listed above. Instead, that decision would be made following a recommendation by FDA's Vaccines and Related Biological Products Advisory Committee and would be based on multiple factors that include:

1) Identification of a drifted virus that has been identified in multiple geographic regions worldwide and is increasing in its frequency of circulation with respect to other viruses within the subtype or lineage;
2) The availability of a candidate vaccine viruses (CVV) with suitable antigenic, genetic, and growth properties;
3) The availability of nucleotide sequences of circulating virus for vaccine development of a licensed recombinant vaccine or use of biosynthetic technologies;
4) Anticipated public health impact of the drifted strain, as determined by the magnitude of antigenic differences, subtype, and antiviral drug susceptibility, among other factors, and the ability of a monovalent vaccine to mitigate that impact;
5) Probability that drifted strain will become predominant in the coming flu season; and
6) Stakeholder consensus (including the Biomedical Advanced Research and Development Authority (BARDA), CDC, FDA, the National Institutes of Health (NIH), the Advisory Committee on Immunization Practices (ACIP), health care providers, and vaccine manufacturers) on the feasibility of an effective deployment, including capacity to produce enough vaccine in time to achieve high coverage before flu season.

In 2014, even if HHS had determined in July that a monovalent vaccine production should have been pursued, it would have been unable to do so because a suitable candidate vaccine virus (CVV) was not available despite CDC's early recognition of the emergence of a drifted H3N2 virus strain. To review the sequence of events that has previously been shared with the Committee:

1) In March 2014, CDC detected five A(H3N2) viruses that were antigenically distinct from the 2014-15 A(H3N2) vaccine component A/Texas/50/2012 and alerted other WHO collaborating centers to look for the antigenic drift variant in other regions of the world. In April and May 2014, CDC detected additional antigenically drifted viruses.
2) In May 2014, CDC began growing a potential candidate vaccine virus strain (A/Palau/6759/2014) that would be more antigenically similar to the drifted virus strain.
3) In June 2014, CDC isolated that candidate vaccine virus strain, and submitted it to New York Medical College (NYMC) for the generation of a high-yield reassortant vaccine virus candidate strain.

4) In July 2014, CDC received a new, egg-grown drifted H3N2 variant A/Switzerland/9715293/2013, and immediately forwarded it to the influenza reassorting lab at NYMC for creation of another potential vaccine candidate virus.
5) In August 2014, CDC performed the preliminary test on A/Palau/6759/2014 to determine whether it could qualify as a candidate vaccine virus. Unfortunately, testing indicated that this strain did not have the characteristics to qualify as a vaccine candidate virus.
6) In September 2014, CDC received a high yielding vaccine candidate virus (A/Switzerland/9715293/2013) from NYMC. CDC then performed its testing on the candidate virus and determined that it qualified as a candidate vaccine virus. On September 26, the WHO recommended the new H3N2 vaccine strain (A/Switzerland/9715293/2013) for inclusion in the Southern Hemisphere vaccine (for 2015).

(b) Under what circumstances would it be appropriate to pursue a monovalent rescue vaccine to respond to a drifted influenza strain?

As part of the efforts to improve public health emergency preparedness for seasonal and pandemic influenza, the Office of the Assistant Secretary for Preparedness and Response (ASPR) coordinates an inter-agency working group called the Flu Risk Management Meeting (FRMM). This group is comprised of HHS senior leaders and influenza subject matter experts. Participating agencies include HHS (ASPR, BARDA, the Assistant Secretary for Health's National Vaccine Program Office, FDA, NIH, and CDC), the Department of Homeland Security, and the Department of Veterans Affairs. The FRMM deliberates policy and programmatic issues regarding influenza medical countermeasures. Discussions include an end-to-end approach from basic research to the advanced development of new medical countermeasures to distribution and utilization strategies.

Recent discussions at the FRMM have included considerations to determine under what circumstances a monovalent rescue vaccine would be pursued due to a drifted seasonal influenza strain. Many factors have been identified that could impact that decision (e.g., manufacturing capabilities, disease severity, etc.) and discussions will continue into the fall to define the triggers for the decision to pursue a monovalent rescue vaccine. Meanwhile, HHS has taken a series of steps to increase the probability that a late season change to tri-or quadrivalent vaccine could be made. These changes would also enable faster production of a monovalent vaccine should it be needed. Newly implemented HHS actions include the following:

1) Enhanced global surveillance of circulating human and avian influenza viruses using existing WHO and CDC systems;
2) More frequent and comprehensive communication with HHS leadership and FDA, and between FDA and the Chair of its Vaccines and Related Biological Products Advisory Committee regarding influenza virus surveillance data, including any evidence for viral antigenic drift and potential seasonal influenza vaccine mismatch;

3) Greater availability of additional vaccine viruses from CDC and other WHO collaborating centers to vaccine manufacturers for seasonal influenza vaccine production; and
4) FDA will begin making potency reagents for new candidate vaccine viruses if surveillance data suggest antigenic drift may be a concern and provide these to vaccine manufacturers if antigenic drift emerges.

Implementation of these actions may reduce the timeline from identification of vaccine mismatch with the circulating virus strain to the availability of a well-matched vaccine. Expanded global surveillance will help identify antigenically drifted strains sooner. Frequent communication on the emergence of antigenic drifts and analysis of the circulating strain with candidate vaccine viruses will help inform decisions on making new vaccines sooner. The greater availability of potential vaccine viruses will help vaccine manufacturers to prepare virus stocks sooner and select those that are well-matched and best for vaccine production. The availability of more potency assay reagents will facilitate the production of new vaccines, if the decision is made to produce a new vaccine strain or new monovalent vaccine.

(c) Are there any contingency plans for a monovalent rescue vaccine in the event of a seasonal influenza vaccine mismatch?

Leadership from the FRMM is engaged in discussions with individual influenza vaccine manufacturers and international partners to solicit their thoughts on potential HHS contingency plans for development of a supplemental monovalent vaccine if antigenic drift and vaccine mismatch occur. HHS convened a meeting in June 2015 with vaccine manufacturers, international public health partners, and HHS representatives to solicit their individual opinions on HHS recommendations and potential plans to address potential seasonal influenza vaccine mismatches due to viral antigenic drift. Several initial proposed actions by HHS for immediate implementation included the following:

1) Work with the WHO to expand influenza strain surveillance capacity that ensures greater and earlier detection of emerging influenza viruses globally that may have drifted antigenicall thereby informing decisions on generating more vaccine viruses sooner.
2) If antigenic drift in a particular virus strain is identified after the WHO and FDA's Vaccines and Related Biological Products Advisory Committee seasonal vaccine strain recommendations are communicated to the manufacturers in February or early March each year, CDC and FDA with WHO should notify the manufacturers of the situation as soon as possible and communicate to HHS senior leadership.
3) If there was evidence of antigenic drift, CDC would develop candidate vaccine seed strains (for egg and cell-based vaccines) that are antigenically similar to the drifted strain and provide the new candidate vaccine viruses to the manufacturers for production testing.
4) In the event of suspected antigenic drift, FDA would develop matched vaccine potency reagents for the new candidate vaccine viruses and make them available to manufacturers.

These and other steps will be tested and further refined in a tabletop exercise planned in November 2015 with HHS agencies and vaccine manufacturers, as individual participants, to solicit their individual opinions. The exercise outcome is expected to inform an HHS action plan for rapid development and manufacturing of a revised seasonal influenza vaccine as a strain change or a separate monovalent vaccine. The FRMM also recommends additional actions items to implement over the immediate, interim, and long-term horizons (18 months – five years) to address vaccine mismatch issues in the areas of virus surveillance and characterization, technologies, vaccine design, and vaccine distribution. Together with the influenza vaccine manufacturers, federal agencies, WHO and its collaborating laboratories, and regulatory authorities and public health leadership in other countries, a coordinated action plan may be adopted to address antigenic drift and vaccine mismatch problems.

5. **A recent CDC study that examined clinician treatment practices for outpatients with influenza during the 2012-2013 season showed that only 16 percent of patients with laboratory-confirmed influenza were prescribed antiviral drugs, while as many as 30 percent were prescribed one of three common antibiotics. In light of such findings, should there be a greater emphasis and timeliness in federal public communications about the use of antiviral medications as a "second line of defense" against seasonal influenza?**

CDC recommendations emphasize that antiviral medication is recommended as early as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness; who require hospitalization; or who are at risk for influenza-related complications. Treatment is most effective when given early in the illness. CDC recommends that providers not delay treatment in these patients until test results become available and should not rely on insensitive assays such as rapid antigen detection influenza diagnostic tests to determine treatment decisions. In addition, because other reviews of randomized control trials (RCT) and observational studies have found consistent clinical benefit of early oseltamivir treatment in reducing the risk of lower respiratory tract complications such as those requiring antibiotics, CDC recommends that persons with uncomplicated influenza who are not in a high risk group and who present within 48 hours of illness onset can be treated with antiviral medications based upon clinical judgment.

Per CDC's April 9, 2015, letter to the Committee, the agency maintains that communicating about antiviral drugs is already a core component of CDC's annual seasonal influenza messaging and guidance. CDC's research does indicate that antiviral drugs are underutilized, which is why it places very heavy emphasis on these communication efforts each year. Qualitative research is underway to better understand why this pattern of underutilization persists and target communications accordingly. While CDC continues to recommend vaccination as an important and still useful preventive measure during a season where there may be or there is reduced vaccine effectiveness, even more emphasis is placed on the use of influenza antiviral drugs for treatment of high risk persons in these seasons. Some of the ways in which CDC communicates about antivirals are as follows:

1) Direct outreach to clinicians (e.g., health alert network messages, clinician outreach and communication activity (COCA) calls);

2) Outreach to clinicians through professional organizations representing those patients at greatest risk (e.g., geriatricians, pediatricians etc.);
3) Outreach to clinicians through mass media (e.g., traditional news media, specialized media like Medscape); and
4) Outreach to public health partners (e.g., weekly situation and recommendation updates).

6. **According to the HHS website, flu.gov, 90 percent of influenza-related deaths and more than half of influenza-related hospitalizations occur in people age 65 and older. Last year's severe influenza season was reportedly the deadliest for seniors in five years. A recent study showed that a new high-dose vaccine was 24.2 percent more effective in preventing influenza in adults 65 years and older relative to a standard-dose vaccine. Another study based on data from more than 2 million Medicare beneficiaries suggests that the high-dose influenza vaccine works better than a standard-dose vaccine for preventing probable influenza illness and influenza-related hospital admissions in elderly people. The study, published by the journal *The Lancet Infectious Diseases*, was funded by the FDA and included authors from that agency as well as from the Centers for Medicare and Medicaid Services and the CDC. The CDC says it has not expressed a preference for either the high-dose or standard vaccine, but that the new findings will be considered in the future policy deliberations of the CDC's Advisory Committee on Immunization Practices (ACIP). CDC told committee staff in a briefing that the high-dose vaccine would not be on the CDC's ACIP agenda until February 2016. In light of these studies, is there any way to expedite consideration of these studies to see if CDC should express a preference on high-dose vaccines?**

   The Advisory Committee on Immunization Practices (ACIP) has recommended high-dose inactivated vaccine (Fluzone HD, Sanofi Pasteur) since its licensure by FDA in 2009 and included the vaccine in the 2010-11 recommendations for use in persons 65 years of ages and older. Adopting ACIP's recommendation, CDC has included Fluzone HD, along with other flu vaccines, in the U.S. influenza vaccine recommendations each season since its approval. Data on the relative efficacy and safety of high-dose vaccine to standard dose vaccines has also been included in CDC outreach to clinicians. At the most recent ACIP meeting on June 24, 2015, a presentation was given which summarized evidence (including the studies referenced in the inquiry) concerning the relative efficacy and safety of high dose and standard dose vaccines for persons 65 years of age and older. Following discussion and consideration of this information, ACIP did not propose a preferential recommendation at that recent meeting. ACIP will continue to review emerging evidence for Fluzone HD as it becomes available. High dose inactivated influenza vaccine remains an appropriate option for persons 65 years of age and older, along with standard dose inactivated influenza vaccine.

7. **The Department's response stated that HHS/CDC purchases and distributes approximately 10 to 15 percent of the total seasonal influenza vaccines available in the United States each year through CDC's Vaccines for Children and Section 317 Immunization Programs. What are the total annual expenditures for seasonal influenza vaccines under these programs? Does HHS/CDC use its purchasing power to require measurement of outcomes for the seasonal influenza vaccines it purchases (i.e., vaccine effectiveness as measured by the degree of match of the vaccine to circulating seasonal**

strains or reductions in deaths or hospitalizations)? If so, what are the measurements, and what have they shown?

CDC's expenditures for seasonal influenza vaccines for the 2014-2015 influenza season were:

1) Vaccines for Children Program: $284,662,004.88; and
2) Discretionary Immunization Program funds (Section 317): $9,481,965.84.

CDC does not require measurement of outcomes as part of the vaccine purchase contracts. However, in addition to vaccine purchase, CDC used appropriated funds for programs that evaluate influenza vaccine effectiveness and influenza vaccine coverage. Vaccine effectiveness and coverage are two key metrics for evaluating and refining U.S. efforts to prevent influenza through vaccination. Through the U.S. Flu Vaccine Effectiveness (VE) Network, CDC has been working with researchers at universities and hospitals since the 2003-2004 flu season to estimate how well flu vaccine works through observational studies using laboratory-confirmed flu as the outcome. The U.S. Flu VE Network currently consists of five study sites across the United States that measure the flu vaccine's effectiveness at preventing outpatient medical visits due to laboratory-confirmed influenza. More information about the U.S. Flu VE Network can be found at http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm. CDC estimates annual influenza vaccination coverage for the United States by utilizing data from several nationally representative surveys: the Behavioral Risk Factor Surveillance System (BRFSS), the National Health Interview Survey (NHIS), and the National Immunization Survey (NIS), and internet panel surveys of adults, health care providers, and pregnant women.

Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2015 are available at: http://www.cdc.gov/flu/pdf/professionals/vaccination/vaccine-effectiveness-table.pdf. This page provides vaccination coverage estimates for 2014-2015: http://www.cdc.gov/flu/fluvaxview/1415season.htm.

Additionally, for FY 2016, CDC has requested $187,558,000 for influenza planning and response, which is level with the FY 2015 enacted level. CDC's influenza planning and response activities include both a comprehensive response for seasonal influenza as well as the ability to respond to an influenza pandemic. CDC's influenza program works to detect, respond to, and prevent influenza disease that can cause mild to severe illness, and at times, death. These annual activities improve preparedness by strengthening surveillance and diagnostic capacity, improving public awareness and provider knowledge about the importance of vaccination, prevention measures, and early treatment, and enhancing our international, federal, state, and local partnerships to respond quickly to influenza epidemics.

8. **Has there ever been an emergency use authorization and/or expanded use authority to allow use of an unlicensed seasonal influenza vaccine?**

An emergency use authorization or an expanded use authority has not been used to allow the use of an unlicensed seasonal influenza vaccine.

DEPARTMENT OF HEALTH & HUMAN SERVICES Office of the Secretary
Washington, D.C. 20201

TO: Secretary Burwell

FROM: Nicole Lurie, ASPR

HHS Influenza Risk Management Group:
Robin Robinson, BARDA
Bruce Gellin, OASH
Carole Heilman, NIH
Jackie Katz, CDC
Karen Midthun, FDA

THROUGH: Andrea Palm
Anne Reid
Averi Pakulis

DATE: May 6, 2015

SUBJECT: Memorandum on Influenza Process Improvements

ISSUE

The mismatched seasonal influenza vaccine in the U.S. during the 2014-2015 season highlights the need to make these vaccines better and sooner. The HHS Influenza Risk Management Group, comprised of HHS staff with expertise in influenza, has been making steady progress toward a goal of universal, highly-effective vaccines through the Influenza Manufacturing Vaccine Initiative (IVMI) -- a partnership between HHS, industry, and academics. Over the past several months the group has been working to understand the mismatch problem in detail, review how both ongoing and new activities might address the mismatch issues, and recommend actions to mitigate this problem in the future.

This memo summarizes the key challenges in the seasonal influenza vaccine development and manufacturing processes, and highlights opportunities for improvement. ASPR is responsible for monitoring and ensuring the implementation of these improvements and providing periodic updates to you.

BACKGROUND

Influenza viruses are constantly changing genetically. This process is known as antigenic drift (drift), and it allows influenza viruses to escape immunity that has built up in the population (stimulated by vaccination or past infection). For this reason, formulation of influenza vaccines may change from season to season to respond to observed changes in circulating influenza virus. Because of the time currently required to produce and distribute influenza vaccines, decisions

regarding which strains to incorporate into the annual seasonal influenza vaccines must be made approximately eight months before the onset of each influenza season. During this time, influenza viruses continue to change, and occasionally, that drift is so significant that it results in influenza vaccines that are a poor match for the predominant virus circulating in the population. In years where the vaccine is well-matched to circulating viruses, vaccine effectiveness is generally between 50 and 70 percent. It is worth noting that in addition to the match between the vaccine and circulating strains, other factors (e.g., health status) can affect how well a vaccine works.

HHS has undertaken a number of activities designed to improve the influenza vaccine development and manufacturing process and increase the likelihood that annual seasonal influenza vaccines are well-matched to the circulating strains, including the following:

- improving global surveillance and virus characterization to detect new emergent strains more quickly;
- incorporating technological improvements to speed production and regulatory timeliness;
- making better, more effective vaccines that would provide broader cross protection across potentially drifted virus strains; and
- improving the systems for distribution, administration, and monitoring of vaccines.

These activities are further detailed below.

Surveillance and Virus Characterization

Globally-coordinated surveillance is the foundation of the influenza vaccine virus selection and development process. Ensuring that the system has the best technologies at its disposal to analyze influenza viruses and contribute to the production of influenza vaccine is equally important. The World Health Organization (WHO) Global Influenza Virus Surveillance and Response System (GISRS) is a global network that provides year-round surveillance of human and animal influenza viruses, makes recommendations on the composition of seasonal influenza vaccines, and provides candidate vaccine viruses for manufacturers to use in the production of seasonal influenza vaccines. CDC and others continue to work to strengthen global surveillance and laboratory detection capacity for influenza viruses, and CDC is in the process of shifting to a new practice that first characterizes viruses by high-throughput nucleotide gene sequencing, affording a quicker and more comprehensive picture of these viruses that can be used early in the process of selecting virus strains for vaccines. In addition, NIAID and BARDA are supporting new evolutionary biology and bioinformatics visualization techniques to investigate drift and the human immune response in order to potentially enhance prediction of which strains are likely to circulate. In the long run, this could increase the likelihood that strains selected for the influenza vaccine are well matched to influenza strains circulating during the influenza season.

Here are the recommendations for surveillance, which agency is accountable for each opportunity, and the timeframe by which activities are anticipated to be completed.

Issues	Recommended Solutions	Responsible Party
Near Term (present-15 months)		
Gaps in global influenza surveillance.	Expand WHO Global Influenza Virus Surveillance and Response System (GISRS) through capacity building.	CDC and WHO (GISRS)
Improve techniques for identification and characterization of antigenic drift viruses.	Expand use of new technologies and optimize alternate assays for testing.	CDC
Mid Term (2-3 yrs.)		
Need for improved understanding of virus antigenicity and vaccine effectiveness to better inform vaccine strain selection.	Change paradigm for vaccine strain selection to include new CDC practice that affords a quicker and more comprehensive picture of these viruses. Develop US public health lab networks to supply whole genome data. Continue to support research on understanding the relationship between antigenic match and vaccine effectiveness.	CDC CDC NIH, BARDA, and CDC
Long Term (4-7 yrs.)		
Reduce time to identify and characterize drifted viruses.	Continue support of novel vaccine strain prediction methods.	NIH, BARDA, and CDC

Technological Improvements

Seasonal influenza vaccine manufacturing and formulation currently takes at least six months from vaccine strain selection in late February to vaccine availability in late August with manufacturers starting production at risk in late December (**see Figure 1**). There have been substantial improvements in the development of high-growth vaccine candidates that increase vaccine manufacturing yields sooner, and the science is continuing to progress rapidly. Vaccine manufacturers are in the process of adopting several process improvements described below for pandemic vaccine. We anticipate, and would ask, that these improvements also be applied to seasonal influenza vaccine manufacturing. **Application of these improvements to seasonal influenza could save four to six weeks in the manufacturing and formulation process; however, until these improvements are used in the seasonal process, we cannot be certain about the exact time savings.** If successful, this could potentially enable final decisions about the vaccine composition to be made with surveillance information closer to the beginning of the influenza season. **We expect these technical improvements may be tested, validated, and adopted by a subset of influenza vaccine manufacturers within two to three years for seasonal influenza vaccines.**

Seasonal influenza vaccines contain either three or four human strains of influenza; these are manufactured separately and combined near the end of the process. How rapidly this can be done depends on candidate vaccine yield (i.e. how much virus is produced in eggs or cells), how quickly the potency assay reagents to test them can be developed, and how rapidly the bulk and formulated vaccine can be tested for potency and sterility and lot released by the FDA. A persistent challenge in candidate vaccine virus production is the need to grow viruses in eggs – the vast majority of influenza vaccines are produced this way. Collaborations between CDC, FDA, WHO, and manufacturers are underway to use synthetic biology (engineering biological systems to increase speed, scale, and precision) and reverse genetics (working backward to make a mutant gene) to accelerate this process. **Generation of high-growth vaccine seeds using these new approaches may save three to five weeks in the initial steps of vaccine production within the next two to three years.**

Through the IVMI initiative, improvements are also being made in the assays that test vaccine before lot release to ensure its potency and sterility. **It is anticipated that this could further decrease vaccine manufacturing time by two to three weeks within the next two to three years.**

Another important issue is how quickly, in the event of a drift in one of the seasonal virus strains, manufacturers could produce a new strain for inclusion in the standard seasonal vaccine or a new monovalent vaccine. Doing this would require manufacturers to have early information about drifted strains, a recommendation from CDC/FDA to make a change, and the ability for potency tests to be available in time for a reformulated vaccine to be released. HHS now uses the Influenza Risk Assessment Tool (IRAT), to decide whether to make limited amounts of vaccine in response to emerging, potentially-pandemic strains. **Using the IRAT as a model, a risk assessment method should be developed by the HHS Influenza Risk Management group within the next 15 months to guide recommendations about whether to change seasonal vaccine strain composition between the WHO recommendation and June.**

It is not clear who would pay for a late-season shift, as seasonal vaccine is made and produced in the private market (unlike in a pandemic where BARDA resources would be available for development). A strong process recommendation resulting from this year's strain mismatch is that following the annual WHO strain selection meeting, FDA and CDC should meet monthly to review early evidence of drift, notify WHO, and be poised to convene an ad hoc meeting of the FDA's Vaccine and Related Biological Products Advisory Committee (VRBPAC) to consider whether to make a recommendation to change strains. In addition, continually improving prediction methods should enable the CDC to provide information to manufacturers regarding which strain(s) give them most concern about potential drift. **Manufacturers could then choose to make that strain last, which would allow them to finalize the composition of the vaccine as late as June (10-12 weeks later than the current process). Communication is key throughout the process, particularly towards late spring/early summer, as discussions with manufacturers suggest that some could also switch a strain in a quadrivalent seasonal influenza vaccine as late as June if they became aware of significant drift.**

Here are the recommendations for technological improvements, which agency is accountable for each opportunity, and the timeframe by which activities are anticipated to be completed.

Issues	Recommended Solutions	Responsible Party
Near Term (present-15 months)		
Need to better facilitate candidate vaccine virus development.	Provide more potential vaccine viruses for production of egg-based candidate vaccine virus (CVVs) and information/viruses to manufacturers. Provide cell-grown seed viruses. Evaluate synthetic biology/genetic engineering to improve antigenic properties of egg-grown CVVs.	CDC, WHO (GISRS), and academic labs producing CVVs
Limited availability of vaccine potency assay reagents to test antigenically-drifted virus strains.	Begin potency assay reagent development early (i.e., at risk) if drifted strains appear to be of concern.	FDA (CBER) and vaccine manufacturers

Issues	Recommended Solutions	Responsible Party
Limited formal evaluation of seasonal influenza antigenic drift risks and remediation.	Develop and apply a risk assessment method to the analysis of seasonal antigenic drift. Convene global partners to communicate risk mitigation steps identified to address late identification of antigenic drift and its impact on seasonal vaccine production.	CDC and FDA HHS Influenza Risk Management Group HHS with global partners
HHS review (other than CDC) of virus surveillance data following WHO/VRBPAC recommendations is limited.	CDC and FDA meet monthly from March through June of each year to review new virus surveillance data, with results communicated to the ASPR and the VRBPAC chair. Convene VRBPAC meeting if strong evidence of drift.	CDC and FDA (CBER) FDA (CBER)
Limited communication with manufacturers on virus antigenic drift possibilities and potential solutions.	Communicate early with manufacturers when antigenic drift is a concern. Convene manufacturers to discuss further additional steps they or the government could take to make strain changes late in the manufacturing process.	CDC and WHO Collaborating Centers with vaccine manufacturers HHS Influenza Risk Management Group with vaccine manufacturers through International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
Virus passaging of candidate virus seeds for high growth may lead to mismatches with circulating virus.	Develop new virus reassortants (combinations) with high-growth potential & match to circulating virus strains.	IVMI initiative (CDC, FDA, NIH, BARDA, and academic and industry partners)
Mid Term (2-3 yrs.)		
Long turnaround for vaccine potency reagents and testing.	Complete work on potency assay development and potency testing methods.	IVMI initiative (CDC, FDA, NIH, BARDA, and academic and industry partners)

Making Better Vaccines

Long-term development and realization of more effective and "universal" influenza vaccines may best address the potential for mismatched seasonal vaccine. **Several promising candidates are anticipated to be ready for NIAID-supported clinical trials in the next two years.** BARDA recently announced a new Request for Proposals to support advanced development of More Effective/Universal Influenza Vaccines that provide broader, longer-lasting immunity to a range of drifted influenza viruses. These vaccines might also provide an important priming response to prepare a population for the emergence of a novel influenza virus, such that only a single dose of pandemic influenza vaccine might be needed if such a virus begins to infect people.

Here is the recommendation for making better vaccines, which agency is accountable for this opportunity, and the timeframe by which activities are anticipated to be completed.

Issues	Recommended Solutions	Responsible Party
Long Term (4-7 yrs.)		
Limited cross protection of current influenza vaccines against drifted viruses.	Continue support of more effective seasonal and universal influenza vaccines.	NIH, BARDA, CDC, and FDA

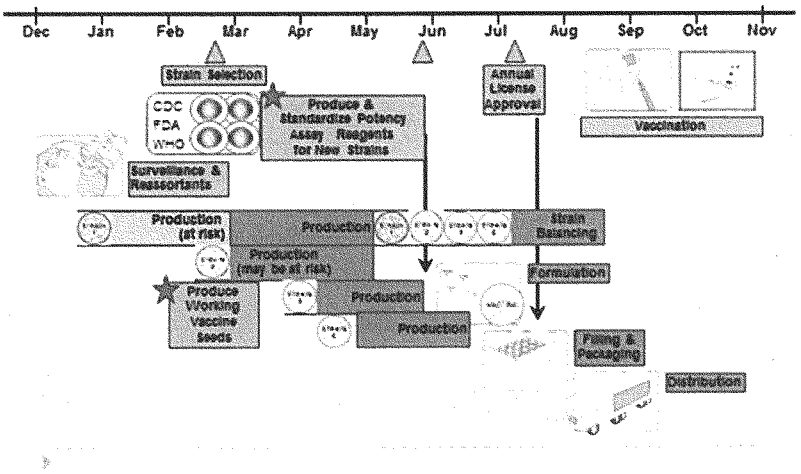
Vaccine Distribution and Administration

It is critical to remember while selecting strains and manufacturing vaccine are complex, so are distribution, administration, tracking, and safety monitoring. Improvements are needed in the vaccine distribution chain so inventory can be tracked throughout and reallocated to address shortages in tracking and vaccine registries, and in adoption of technologies such as radio frequency identification (RFID) technology for vaccine vials, containers, and packaging, so that vaccine can be monitored, tracked, and more easily be evaluated for safety and efficacy. Some of these improvements are underway as part of pandemic preparedness.

Here is the recommendation for vaccine distribution, which agency is accountable for this opportunity, and the timeframe by which activities are anticipated to be completed.

Issues	Recommended Solutions	Responsible Party
Mid Term (2-3 yrs.)		
Limited visibility on vaccine distribution, tracking, and monitoring.	Continue improvements to vaccine distribution, tracking, and monitoring.	CDC, FDA, and BARDA

Figure 1. Seasonal influenza vaccine strain selection, manufacturing, and vaccination steps for the U.S. market with on-going improvement projects in manufacturing.



Red stars (★) indicate the on-going projects to improve and expedite influenza vaccine manufacturing through the IVMI initiative. The gray triangles indicate current time of strain selection and bulk manufacturing completion and annual license approval. The period from strain selection to completion of production represents the period in which a strain change might occur if needed.

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
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Majority (202) 225–2927
Minority (202) 225–3641

December 10, 2015

Dr. Anne Schuchat
Principal Deputy Director
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30329

Dear Dr. Schuchat:

Thank you for appearing before the Subcommittee on Oversight and Investigations on Thursday, November 19, 2015, to testify at the hearing entitled "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?"

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Thursday, December 24, 2015. Your responses should be mailed to Greg Watson, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to Greg.Watson@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Tim Murphy
Chairman
Subcommittee on Oversight and Investigations

cc: Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachment

Energy and Commerce Committee Hearing: U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?
Questions for the Record

1. **What role does health IT play in helping improve health coordination?**

Health IT supports a variety of coordination, tracking and reminder functions for both the provider and public health levels. The provider level functions focus on patient care and outcomes such as providing consolidated immunization histories for use in determining appropriate client vaccinations. At the public health level, CDC's National Center for Immunization and Respiratory Diseases (NCIRD) supports the development of Immunization Information Systems (IIS). IIS supports analytics by providing aggregate data on vaccinations for use in surveillance and program operations, and in guiding public health action with the goals of improving vaccination rates and reducing vaccine-preventable disease. IIS are confidential, population-based, computerized databases that participating vaccine providers can use to record immunization doses administered. Use of IIS is important since having a record of vaccinations is needed for school entry, college entrance, working in health care settings, military service, and to ensure patients are up-to-date on recommended vaccinations. In addition, vaccination recommendations are complex, and change over time, so having an up-to-date record is key to knowing which vaccines are needed and ensuring patients receive the right vaccines at the right time, and are neither over-vaccinated (get too many doses) nor are missing vaccines. Patients may also seek care from several different providers so the IIS serves as a central source of information on which vaccines a patient received from other medical providers, pharmacies, or other locations such as work place, mass vaccination, or hospital settings. NCIRD has also supported advancements in a vaccine ordering system called VTrckS to improve efficiencies in the vaccine ordering and distribution network at the Federal, state/local, and vaccination provider levels. Finally, advances in health IT have led to the addition of two-dimensional (2D) barcodes on many vaccines which can be scanned and assist providers in documenting key data elements of the vaccination record such as lot number, expiration date, and product identification. These advances can aid providers in more quickly and accurately documenting administered vaccines which further strengthens health coordination.

2. **What is the CDC's role in supporting public health agencies and encouraging bidirectional communication with physicians? Since the Meaningful Use program requires physicians to e-prescribe and to input immunization data into registries what are the capabilities for bidirectional communication from pharmacies and public health departments back to physicians?**

CDC provides support through a variety of mechanisms to 56 U.S. immunization programs housed within state and local public health departments; all but one of these immunization programs (New Hampshire) operate Immunization Information Systems (IIS). CDC leads the development and publication of health IT communication standards for immunizations that facilitate effective bi-directional communication between IIS, electronic medical records, and other health IT systems. CDC provides financial support and technical assistance to immunization programs to implement current health IT standards for bi-directional exchange, and to identify and enroll vaccination providers in the IIS to facilitate data exchange. Approximately 90 percent of IIS have the capability to receive immunization information from electronic medical records consistent with Meaningful Use messaging standards; approximately half of the IIS are engaged in bi-directional data exchange. These efforts have helped to support not only the CDC program but also the Office of the National Coordinator for Health IT interoperability initiatives. A 2014 survey found that pharmacies were reporting doses administered to IIS in 36 of the 45 immunization programs that responded (80 percent); pharmacies were required to report to IIS in 22 jurisdictions (49 percent). This survey found almost no pharmacy capability for bi-directional communication with IIS. However, as vaccinations are reported to IIS from pharmacies, they become available to clinicians as part of the immunization history, upon which clinical decisions can be made.

Energy and Commerce Committee Hearing: U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?
Questions for the Record

3. **Some physicians report that submitting data to their state registries is seamless while others say that they must input data manually or that a few states do not have much of a registry at all. How would you describe interoperability among state registries?**

Technical and operational capacities vary tremendously among IIS, electronic medical record systems, and other health IT systems. Inconsistent implementations result in limited data exchange. As mentioned in response to question 2, approximately 90 percent of IIS have the capability to receive immunization information from electronic medical records (EMRs) and other health IT systems consistent with Meaningful Use messaging standards; approximately half of the IIS are engaged in bi-directional data exchange with EMRs. As of 2014, almost no pharmacy capability for bi-directional communication with IIS existed. Policies that impact data sharing between providers and IIS also vary at the state and local level. A 2012 survey found that explicit consent was required in three states (Kansas, Montana, and Texas) to share childhood immunization information from a provider to an IIS, and in eight states it is required for adult immunization information.

CDC and its partners are committed to overcoming barriers in the registry community. An IIS Executive Board, comprised of Federal, state, and local government stakeholders, was established at CDC to support prioritization and development of IIS initiatives to improve interoperability and other key outcomes. Examples of initiatives recently launched include targeted technical assistance to immunization programs that require assistance to overcome local barriers to IIS success and the identification of non-technical barriers that limit IIS data accuracy, use and exchange. With continued support from and collaboration between Federal, state, local, and private-industry stakeholders, barriers to effective interoperability between IIS and other health IT systems can be overcome.

FRED UPTON, MICHIGAN
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RANKING MEMBER

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2125 RAYBURN HOUSE OFFICE BUILDING
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Majority (202) 225-2927
Minority (202) 225-3641

December 10, 2015

Dr. Robin Robinson
Director, Biomedical Advanced Research and Development Authority
Office of the Assistant Secretary for Preparedness and Response
200 Independence Avenue, S.W.
Washington, DC 20001

Dear Dr. Robinson:

Thank you for appearing before the Subcommittee on Oversight and Investigations on Thursday, November 19, 2015, to testify at the hearing entitled "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?"

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

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Sincerely,

Tim Murphy
Chairman
Subcommittee on Oversight and Investigations

cc: Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the Assistant Secretary
for Preparedness & Response
Washington, D.C. 20201

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
United States House of Representatives
Washington, D.C. 20515

Dear Chairman Murphy:

Thank you for the opportunity to address your questions from the November 19, 2015 hearing before the Subcommittee on Oversight and Investigations entitled "U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved." As the Acting Director of the Biomedical and Advanced Research and Development Authority (BARDA), I will be addressing your questions as the former BARDA Director, Dr. Robin Robinson, resigned in March 2016.

Given the significant threat posed by seasonal influenza, developing more effective influenza vaccines remains a top priority for the Assistant Secretary for Preparedness and Response (ASPR). The safety and well-being of the American people is of the utmost importance and I can assure you that BARDA will continue our work to improve pandemic influenza preparedness. This includes acquiring a broad array of medical countermeasures for pandemic influenza, including vaccines, therapeutics, diagnostics, and non-pharmaceutical countermeasures.

I thank you again for your letter and I look forward to continuing our work with you and the committee. I have enclosed a detailed response to the questions presented for the record after the hearing concluded. If you have any additional questions, please do not hesitate to contact me at [redacted]

Sincerely,

[redacted]

Richard J. Hatchett, M.D.
Acting Director, BARDA

Enclosure

QUESTIONS FOR THE RECORD

HOUSE ENERGY AND COMMERCE SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?
THURSDAY, NOVEMBER 19, 2015

ROBIN ROBINSON, PHD
DIRECTOR, BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY (BARDA)
DEPUTY ASSISTANT SECRETARY FOR PREPAREDNESS & RESPONSE (ASPR)
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)

Rep. Blackburn

1. **In light of the ongoing public health challenges associated with pandemic influenza, do you expect this PREP Act declaration to be extended, and if so, when will it be extended?**

The Secretary of Health and Human Services signed the Public Readiness and Emergency Preparedness (PREP) Act declaration on Dec. 1, 2015 to provide liability protection for the distribution of certain countermeasures that address pandemic influenza and other biothreats. The declaration was published in the Federal Register on Dec. 9, 2015, became effective on Jan. 1, 2016, and is scheduled to expire on Dec. 31, 2022. Any consideration of an extension beyond this point would be evaluated at a later point in time.

Rep. Tonko

1. **How is BARDA assessing its current investments to ensure that you are fully leveraging the capacity that we have here in the United States for delivering these cutting edge technologies as quickly and effective as possible? And, what can we do in Congress to enhance your ability to meet these goals?**

A member of the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), ASPR/BARDA uses a number of different methods to evaluate current and future investments for the development, procurement, production, and delivery of medical countermeasures. PHEMCE subject matter experts and industry partners help us conduct In-Process Reviews (IPR) for medical countermeasure (MCM) development projects concerning pandemic influenza. IPRs are conducted at key milestones to inform investments and evaluate performance. Internally, we manage annual program and portfolio reviews with our Scientific Board of Advisors to ensure that we are meeting our strategic goals and advancing national pandemic goals. With our PHEMCE colleagues, especially the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Vaccine Program Office (NVPO), and the National Institutes of Health (NIH), we participate in periodic meetings, workshops, and exercises on seasonal and pandemic influenza to address MCM planning and other issues. MCM planning and budgets for pandemic influenza are incorporated into the overall PHEMCE governance process.

The PHEMCE, conducts quarterly reviews to determine progress and identify challenges relative to the PHEMCE Strategic and Implementation Plan. The PHEMCE-wide pandemic influenza MCM portfolio reviews MCMs for other biothreats on an 18-month cycle.

The FY 2017 President's Budget request for pandemic influenza is $125 million. Providing support at that level will help ensure the development of more effective seasonal and pandemic influenza vaccines, including potential universal vaccines that can provide protection against all influenza strains. In addition, supporting the program at the requested level will allow HHS to continue improving the influenza vaccine manufacturing process so more vaccines are available sooner. It will also allow the development of novel immunotherapeutics and next-generation antiviral drugs to treat critically-ill persons with influenza; allow the development and implementation of new rapid nucleotide sequencing technologies for virus surveillance and diagnostics, including the potential for self-administered diagnostics for home detection of influenza; and would sustain and expand national stockpiles of pre-pandemic influenza vaccines and antiviral drugs.

Rep. Green

1. **With the understanding that it takes a realistic amount of lead time to produce the products necessary to administer vaccines and address an outbreak on a large scale, do you believe that we are in a position to respond today to the needs of 300 million Americans in the event of a pandemic?**

Yes. The United States is more capable of developing, manufacturing, testing, and delivering needed vaccines, antiviral drugs, and diagnostics to meet the demands of an influenza pandemic than ever before. Investments in modern influenza vaccine technologies have led to the licensure of new cell and recombinant-based influenza vaccines by the Food and Drug Administration (FDA). Through this advancement we can expedite manufacturing, including influenza vaccines with adjuvants that can provide more vaccine with less vaccine antigen (antigen-sparing) and greater cross-protection against antigenically-different virus strains. Using new vaccine technologies, combined with our Centers for Innovation in Advanced Development and Manufacturing Fill Finish Manufacturing Network, domestic pandemic influenza vaccine manufacturing capacity has grown from 50 million doses in 2005 to more than 500 million doses in 2015. New technologies like reverse genetics, synthetic biology, and digital sterility assays has shortened the time frame for available pandemic influenza vaccines by 15 to 20 percent. Through multiple exercises and workshops, federal, state, and local partners have honed national response plans for manufacturing, distributing, and administering pandemic influenza vaccines.

Antiviral drug stockpiles for influenza are maintained at levels to treat at least 20 percent of the United States population. Since 2009, one new influenza antiviral drug has been approved by the FDA and may be administered as a single treatment. In addition, new immunotherapeutic therapeutic candidates are under development, which did not exist in 2009.

In terms of scientific advancement, more than 10 point-of-care and high-throughput polymerase chain reaction (PCR)-based and lateral flow antibody-based rapid diagnostic assays have been developed, approved by the FDA, and marketed in the U.S. to detect influenza in clinical samples. Many of the high-throughput assays are implemented in the U.S. Laboratory Response Network. In addition, many of these diagnostics are multiplex assays that can detect not only human and animal influenza viruses but also other respiratory pathogens that may present as influenza-like illnesses.

HHS is reviewing the HHS Pandemic Influenza Plan (2005) and preparing a revised plan that acknowledges our progress in MCM development and will incorporate lessons learned from the 2009 H1N1 pandemic and other influenza outbreaks. The revised plan will incorporate new advancements in influenza vaccines, antivirals, diagnostics, and other surveillance and control measures. It will also introduce new technologies to help treat, prevent, and minimize the impact of an emerging pandemic. Together, new goals will be enumerated for U.S. pandemic influenza preparedness and response in alignment with global goals and plans. The new HHS Pandemic Influenza Plan is slated for release in late 2016.

2. **What has BARDA learned from the H1N1 outbreak of 2009? Specifically, what steps have been taken as a result of lessons learned to ensure that we now have the appropriate number of drug delivery devices either to vaccinate or administer therapies in response to a large scale outbreak of influenza?**

In 2010, HHS and the President's Council of Advisors on Science and Technology (PCAST) made recommendations based on the 2009 H1N1 pandemic to improve pandemic influenza preparedness and response planning with regards to medical countermeasures. Subsequent exercises were conducted by HHS and others resulting in the HHS H1N1 lessons learned report (2013). In terms of medical countermeasures, important lessons learned included the need to expand access to more nimble and flexible domestic vaccine manufacturing capabilities utilizing new technologies such as cell- and recombinant-based vaccine manufacturing platforms, reverse genetics and synthetic biology, new methods for candidate vaccine strain generation, potency assays, and sterility assays. Key to these developments was public-private partnerships with industry, academics, and non-government organizations including the World Health Organization. Cost-sharing between HHS and industry partners was integral for this expansion, which included building new and retrofitting existing U.S.-based vaccine manufacturing facilities. Another key lesson concerned the need for constant, accurate, and seamless communication among HHS vaccine partners (ASPR, the Centers for Disease Control and Prevention (CDC), and FDA), vaccine manufacturers and distributors, and state and local health care providers.

ASPR/BARDA and CDC maintain stockpiles of ancillary supplies (i.e., needles, syringes, etc.) to administer vaccines and other products for pandemic influenza and other public health emergencies. Further, ASPR/BARDA has maintained contracts with major syringe and needle manufacturers since 2009 to supply these products. These contracts may be utilized at any time to expand the manufacture and delivery of these ancillary supply stockpiles. The 2009 contracts ensured that every H1N1 vaccine dose distributed in the U.S. was accompanied by the appropriate ancillary supply kit.

3. **After such a poor vaccine in the 2014-2015 season, what are each of your agencies doing in terms of outreach to combat the perception that the flu vaccine doesn't work? What efforts are being made to inform people on the importance of vaccination and the utility of the vaccine itself?**

ASPR/BARDA has led PHEMCE efforts to review, coordinate, and prepare action plans with FDA, CDC, the National Institutes of Health (NIH), and the National Vaccine Program Office (NVPO), as well as industry, academia, and other international influenza and vaccine experts, to minimize and address the effects of future late-season influenza virus antigenic drifts and seasonal influenza

vaccine mismatches. Last summer, members of the national and international scientific and public health community were convened by HHS and provided a number of specific recommendations to address near- and long-term influenza vaccine mismatch issues. Many of the recommendations called on HHS to focus on five areas: Timeliness of surveillance, candidate vaccine virus development and characterization, reagent preparation, vaccine production, and tracking vaccine distribution. We have discussed this plan with public health, scientific and industry stakeholders and have reviewed these seasonal influenza vaccine issues and risk mitigation plans at international scientific and professional medical organization meetings. These recommendations reinforce our long-term goals to develop more effective seasonal and pandemic influenza vaccines with universal potential. These plans were presented at BARDA Industry Day (October 2015) and at the PHEMCE Stakeholders Workshop (January 2016).

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